제21회

부산경남내과학회 및
대한내과학회 평생교육
연수강좌

INTERVAL CANCER OF COLON
중간 대장암

Division of gastroenterology

Department of internal medicine

Dong Hoon Baek

목차

❖ Detection of CRCs

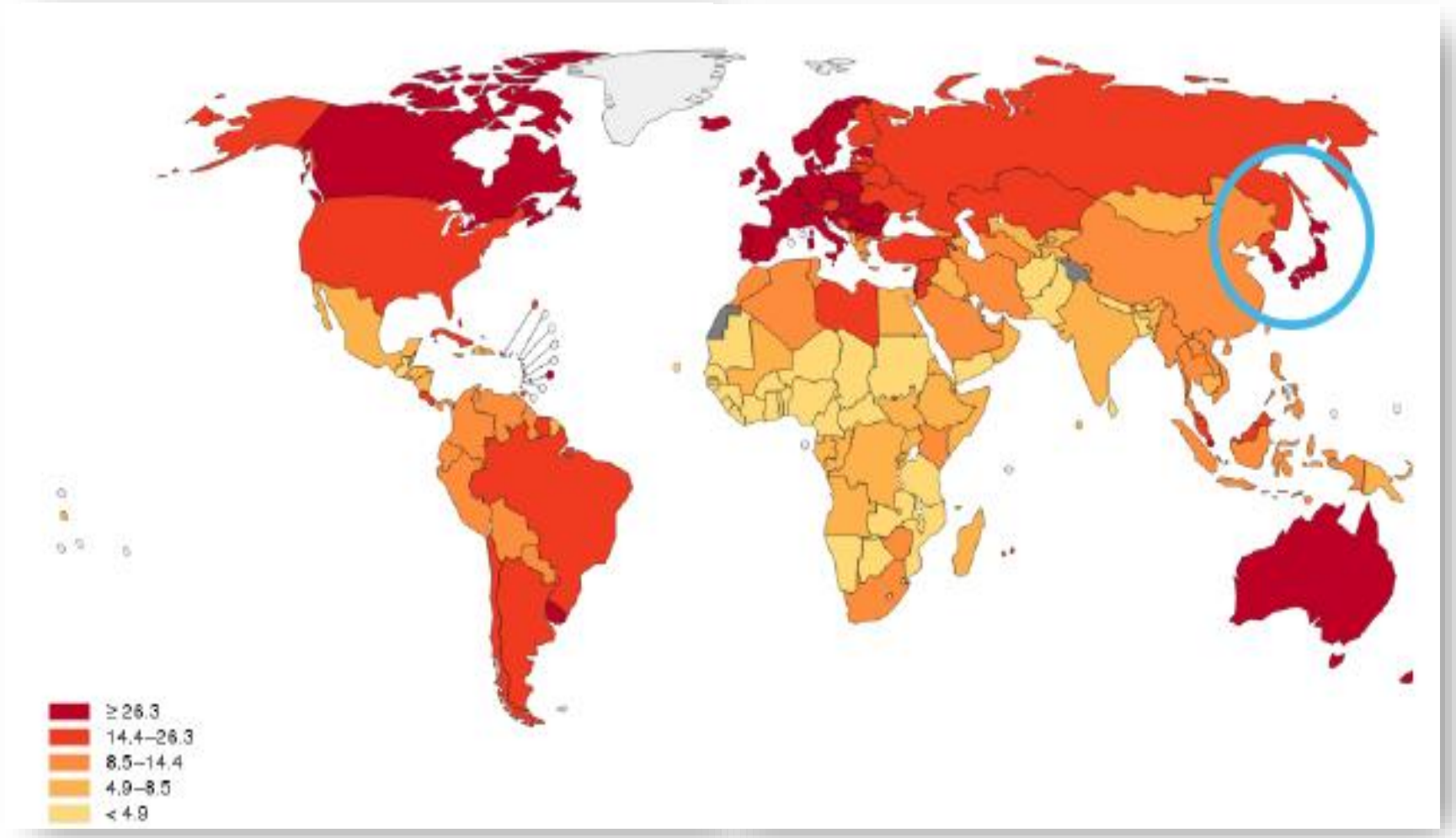
: Prevalence & Screening

❖ Interval colon cancer

- Definition & Taxonomy
- Prevalence & Risk & Outcome
- Characteristics
- Cause
- Prevention

목차

대 장 암 - 2015년 국가암등록통계 (2017.12.21)



40~49세
29 / 10만명

50~59세
83 / 10만명

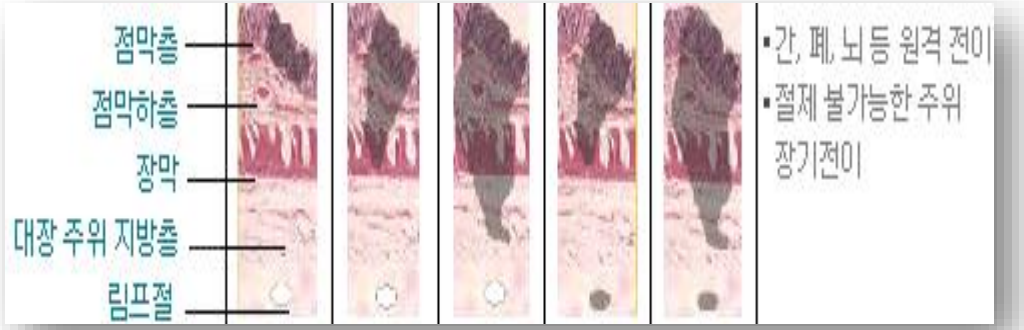
60~69세
174 / 10만명

대 장 암

표 2. 대장암 5년 상대생존율 국제 비교 (단위: %)

	한국('08-'12)	미국('04-'10)	캐나다('06-'08)	일본('03-'05)
전체	74.8	64.7	64.0	69.2

출처: 2012년 국가암등록통계 자료(2014)



localized : 5YSR

94.5%

metastatic : 5YSR

18.6%

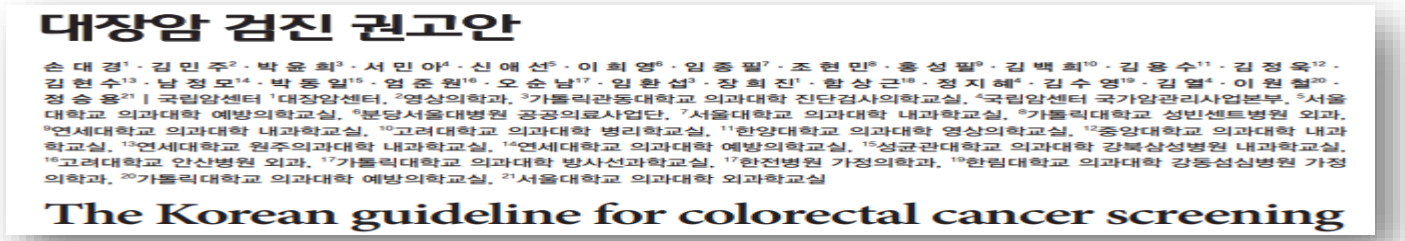
대 장 암 screening

stool occult blood test

Colonoscopy

	ACG (2009)	ACP (2015)	NCCN (2015)	USPSTF (2016)	ACS (2016)
Sigmoidoscopy (yr)	Q 5-10	Q 5	Q 5	Q 5 or Q 10 + stl	Q 5
Colonoscopy (yr)	Q 10	Q 10	Q 10	Q 10	Q 10
CT colonography (yr)	Q 5	N/A	N/A	Q 5	Q 5
Ba enema (yr)	N/A	N/A	Q 5	N/A	Q 5
Stool eFOBT (yr)	Q 1	Q 1	Q 1	Q 1	Q 1
Stool FIT (yr)	Q 1	Q 1	Q 1	Q 1	Q 1
Stool MT-sDNA (yr)	N/A	N/A	N/A	Q 1-3	Q 3

대 장 암 screening : 1. SOBT



대장암 검진 권고안

손 대 경[1] · 김 민 주[2] · 박 윤 희[3] · 서 민 아[4] · 신 애 선[5] · 이 희 영[6] · 임 종 필[7] · 조 현 민[8] · 홍 성 필[9] · 김 백 희[10] · 김 용 수[11] · 김 정 욱[12] · 김 현 수[13] · 남 정 모[14] · 박 동 일[15] · 엄 준 원[16] · 오 순 남[17] · 임 환 섭[3] · 장 희 진[1] · 함 상 근[18] · 정 지 혜[4] · 김 수 영[19] · 김 열[4] · 이 원 철[20] · 정 승 용[21] | 국립암센터 [1]대장암센터, [2]영상의학과, [3]가톨릭관동대학교 의과대학 진단검사의학교실, [4]국립암센터 국가암관리사업본부, [5]서울대학교 의과대학 예방의학교실, [6]분당서울대병원 공공의료사업단, [7]서울대학교 의과대학 내과학교실, [8]가톨릭대학교 성빈센트병원 외과, [9]연세대학교 의과대학 내과학교실, [10]고려대학교 의과대학 병리학교실, [11]한양대학교 의과대학 영상의학교실, [12]중앙대학교 의과대학 내과학교실, [13]연세대학교 원주의과대학 내과학교실, [14]연세대학교 의과대학 예방의학교실, [15]성균관대학교 의과대학 강북삼성병원 내과학교실, [16]고려대학교 안산병원 외과, [17]가톨릭대학교 의과대학 방사선과학교실, [18]한전병원 가정의학과, [19]한림대학교 의과대학 강동성심병원 가정의학과, [20]가톨릭대학교 의과대학 예방의학교실, [21]서울대학교 의과대학 외과학교실

The Korean guideline for colorectal cancer screening

SOBT

45~80세의 평균위험군에서 대장암의 선별검사로 기존의 guaiac 대변잠혈검사에 비해 대변 면역화학검사를 우선적으로 권고.

	대장암진단 민감도	대장암진단 특이도
guaiac SOBT	79.4%	88.1%
FIT	73%	94.8%

대장암 사망율 감소 : 15~33%

N Engl J Med 2000;343:1603-1607.
Cancer Detect Prev 2007;31:3-11.

대 장 암 screening : 2. 대장내시경

Korean J Gastroenterol Vol. 59 No. 2, 65-84
http://dx.doi.org/10.4166/kjg.2012.59.2.65

SPECIAL REVIEW

KjG

대장암 선별과 대장폴립 진단검사 가이드라인

Colonoscopy

50세 이상의 평균위험군에서 대장암 선별과 대장샘종의 진단 검사로 대장내시경검사를 우선적으로 권고한다.

- 중대한 합병증의 발생률 : 0~0.47%
- 사망의 발생률 : 0~0.06%

	Adenoma Cohort			General Population			
Follow-up Time	No.	Person-Years at Risk	Observed Deaths	Expected Deaths	SMR (95% CI)	Reduction	P Value
			no.	no.		%	
All	2602	37,073	12	25.4	0.47 (0.26–0.80)	53	0.008
<10 yr	2602	22,903	4	9.1	0.44 (0.14–1.06)	56	0.09
≥10 yr	2031	14,170	8	16.3	0.49 (0.23–0.93)	51	0.04

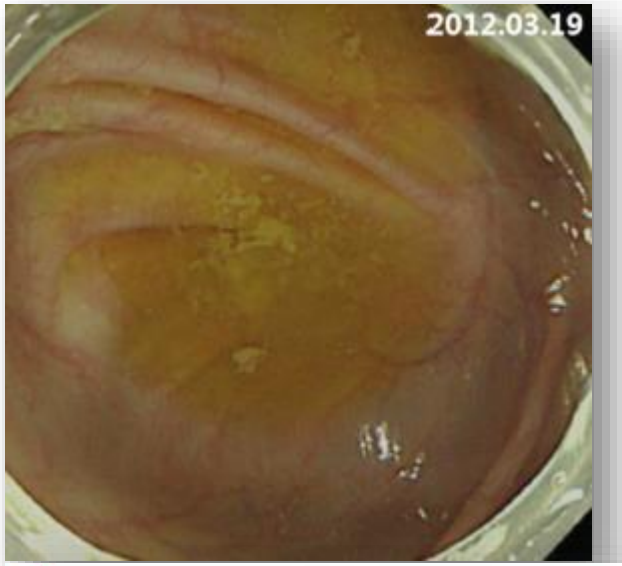
대장암 발생율 감소 : 76~90%

대장암 사망율 감소 : 65%

N Engl J Med 1993;328:901-906.
CGH 2009;7:770-775.

목차

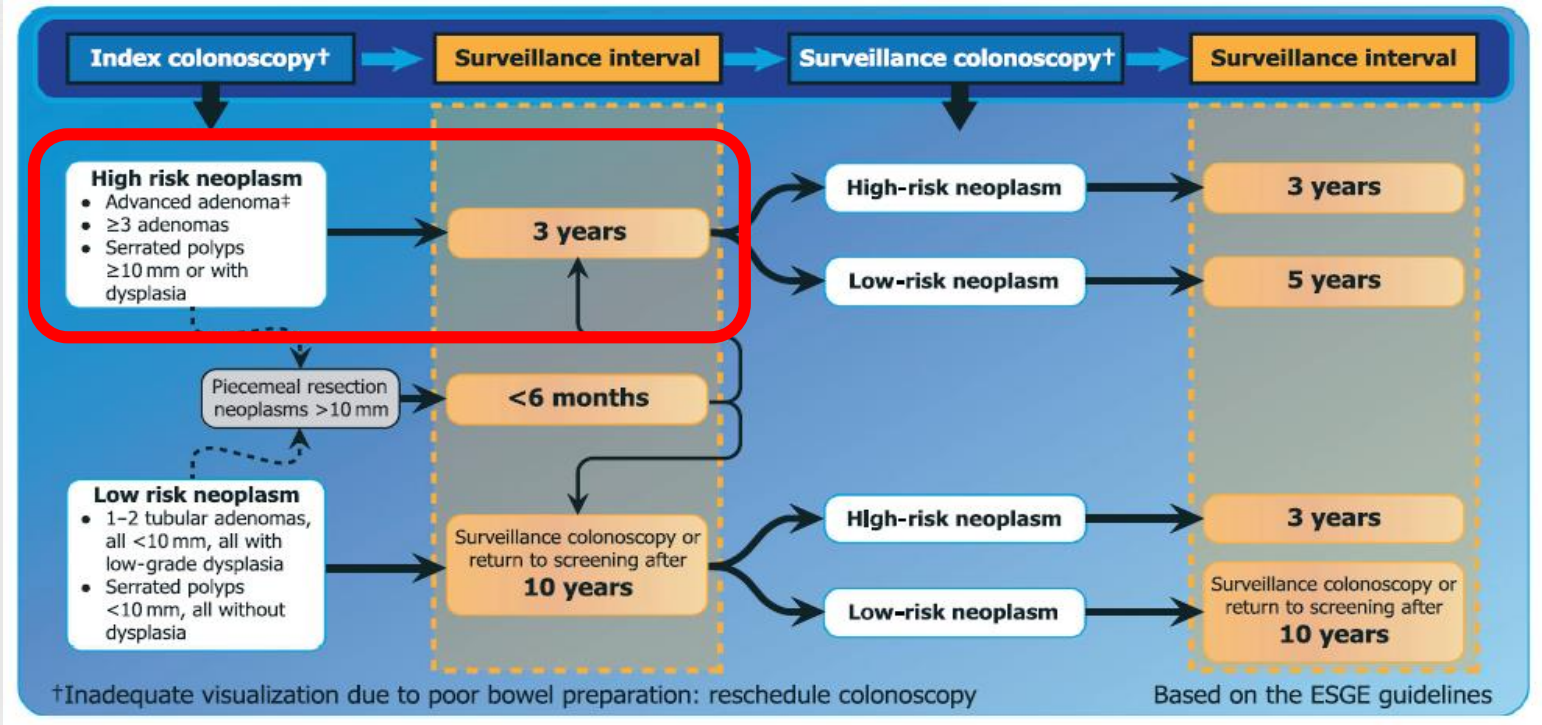
Case - Interval cancer



No abn`l finding on A.C

10mm 이상, 4개의 LGD

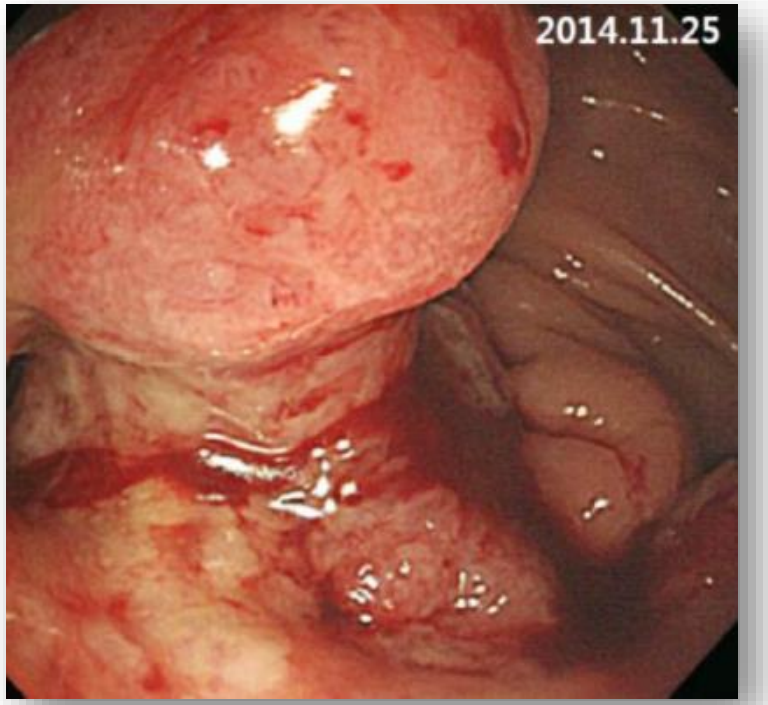
on Rectosigmoid lesion



Korean J Gastroenterol, 65;5
Digestive Endoscopy 2016; 28: 348–359

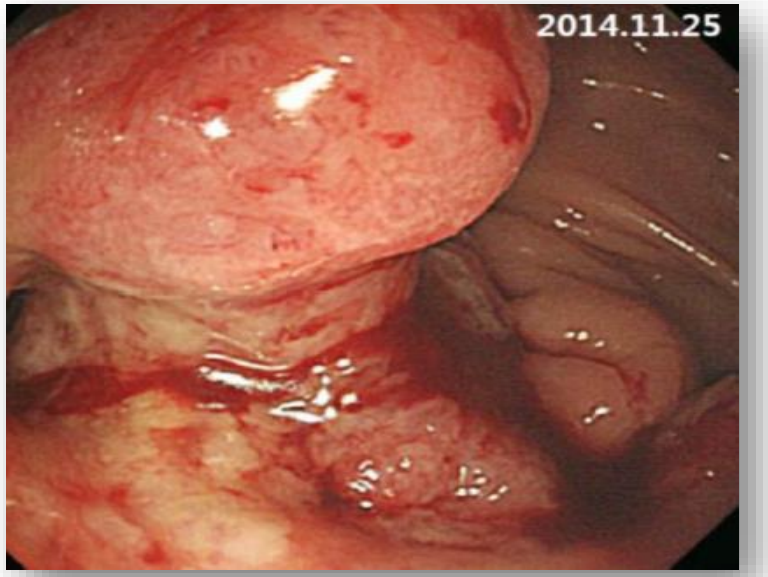
Case - Interval cancer

2년 후 Anemia, RLQ pain



Korean J Gastroenterol, Vol. 65 No. 5, May 2015

Case - Interval cancer



2012.3.19

2014.11.25

2015.3.19

High risk

중간 대장암

Interval cancer of colon

Postcolonoscopy colorectal cancers (PCCRC)

Failure of colonoscopy to detect colorectal cancer: evaluation of 47 cases in 20 hospitals

GASTROINTESTINAL ENDOSCOPY
VOLUME 45, NO. 6, 1997

Joseph H. Haseman, MD, Gregory T. Lemmel, MD, Emad Y. Rahmani, MD, Douglas K. Rex, MD

Indianapolis, Indiana

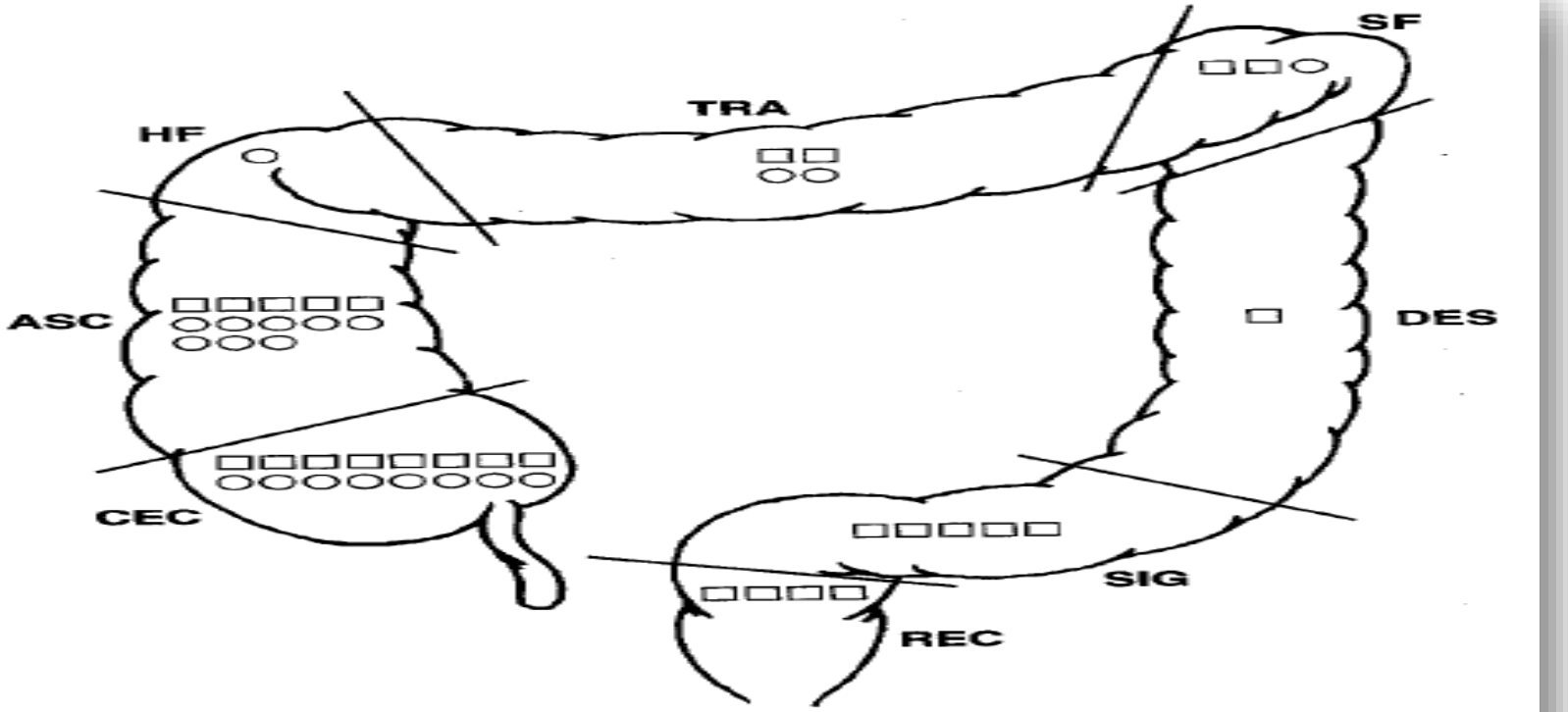
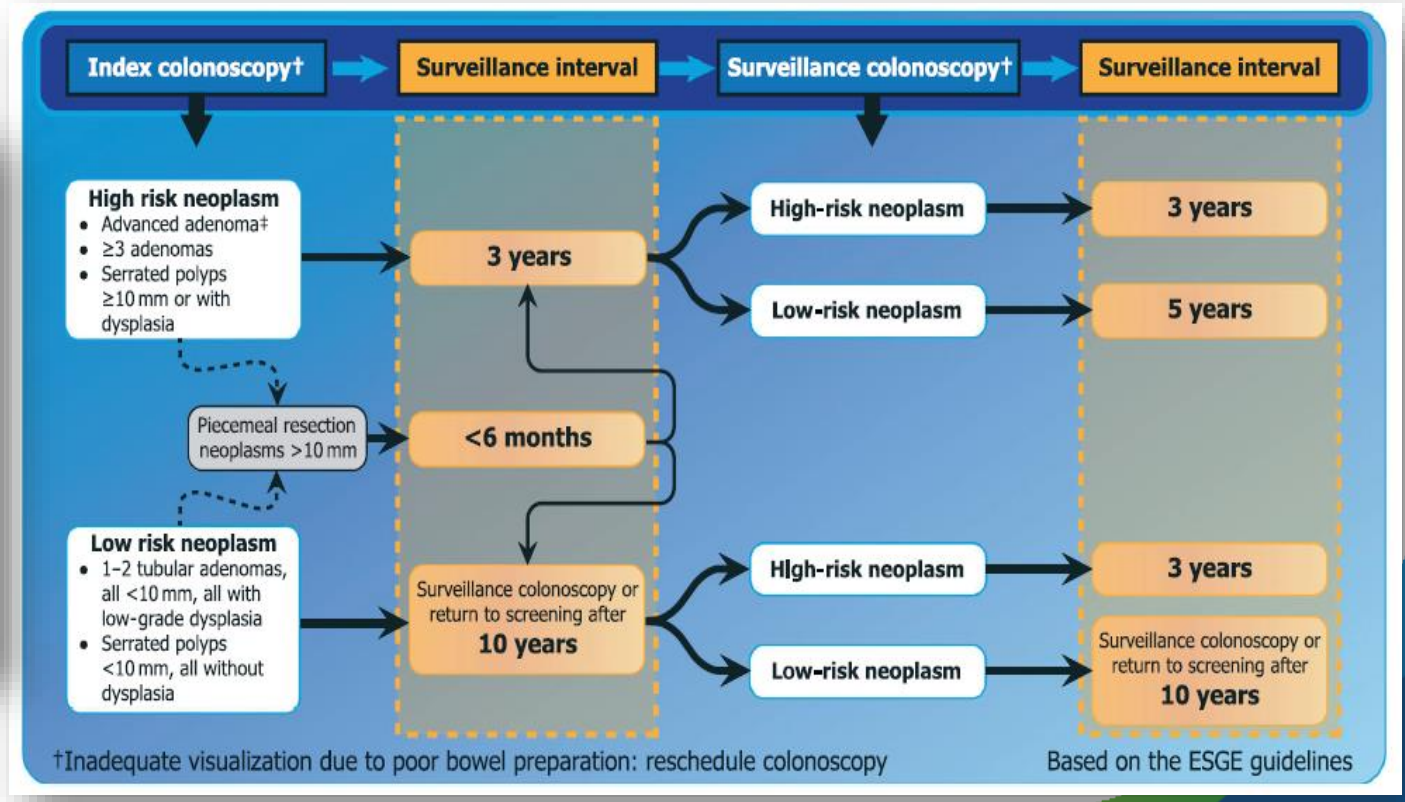


Figure 1. Location of colorectal cancers "missed" (□) and "not reached" (○). *CEC*, Cecum; *ASC*, ascending; *HF*, hepatic flexure; *TRA*, transverse; *SF*, splenic flexure; *DES*, descending; *S*, sigmoid; *REC*, rectum.

Study	Subjects	Prevalence	Major findings
Farrar et al.[14] (2006)	Clinical record of veterans (n=830)	5.4%	27% of interval cancers developed at previous polypectomy segments
Bressler et al.[15] (2007)	Claims-based administrative data (n=31,074)	3.4%	2.1% in the left colon vs. 5.9% in the right colon
Lakoff et al.[16] (2008)	Claims-based administrative data (n=111,402)	1.3% vs. 2.2%	Negative colonoscopy has a protective effect for CRC (1.3% vs. 2.2%)
Kahi et al.[8] (2009)	Asymptomatic screening cohorts (n=715)	1.7%	48-67% CRC reduction with screening colonoscopy
Kaminski et al.[17] (2010)	National CRC screening program in Poland (n=45,026)	0.09%	Association of interval cancer risk with ADR
Mulder et al.[18] (2010)	Administrative primary care data (n=457,014)	2.9% vs. 4.4%	Protective effect with previous examinations for CRC (2.9% vs. 4.4%)
Singh et al.[12] (2010)	Manitoba Cancer Registry database (n=4,833)	7.9%	4.5% in the left colon vs. 14.4% in the right colon
Singh et al.[19] (2010)	Manitoba database (n=45,985)	3.0%	0.6% in the left colon vs. 2.1% in the right colon
Baxter et al.[20] (2011)	Claims-based administrative & cancer registry (n=14,064)	9.0%	6.8% in the left colon vs. 12.4% in the right colon
Cooper GS et al.[11] (2012)	SEER database (n=57,839)	7.2%	2.9% in the left colon vs. 4.9% in the right colon
Brenner et al.[21] (2012)	Population-based case-control study (CRC n=1,945)	4.0%	Substantial proportion of interval cancers are due to missed lesions
Horiuchi et al.[22] (2012)	Single center colonoscopy registry (n=3,212)	0.3%	2.3% in the left colon vs. 13.3% in the right colon, Japanese data
Huang et al.[23] (2012)	Post-polypectomy surveillance data (n=1,794)	0.8%	2.9 cases/1,000 person-year in follow up colonoscopy
Kim et al.[24] (2013)	Single center CRC registry (CRC n=482)	6.2%	2.5% in the left colon vs. 3.3% in the right colon, Korean data
Erichsen et al.[25] (2013)	Population-based cohort study (CRC n=36,686)	2.6%	Majority interval cancers may be missed lesions, without aggressive biology
Samadder et al.[26] (2014)	Population-based study (n=126,851, CRC n=2,659)	6.0%	Right colon location (OR 2.24) family history of CRC (OR 2.27)

Colorectal cancer diagnosed after a colorectal screening examination or test in which no cancer is detected, and before the date of the **next recommended exam**.



Digestive Endoscopy 2016; 28: 348–359

I. Definition and Taxonomy

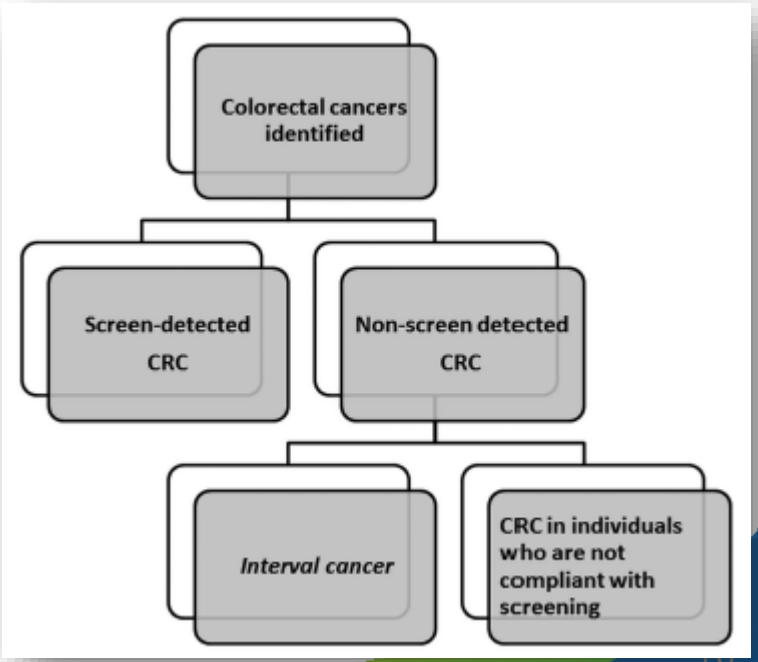
Colorectal cancer diagnosed after a colorectal screening examination or test in which no cancer is detected, and before the date of the next recommended exam.

- **(1) Screen-detected CRC**

  : cancers diagnosed within the screening programme, and at a defined period after a positive screening test/examination

- **(2) Non-screen-detected CRC**

  : cancers in individuals who are not compliant with screening



Gut 2014

- FIT screen-detected cancer
- FIT interval cancer
- CS interval cancer

FIT screen-detected cancer

- 60세 여자. **annually FIT**
- **2년 전**까지 2회의 annual FIT 검사 **negative**
  (last screening : 2016.3월)
- **2017.3월 FIT 검사 positive**
  => **대장내시경** 시행 후 **대장암** 진단받음.

FIT interval cancer

CS interval cancer

FIT screen-detected cancer

FIT interval cancer

- 57세 남자. **annually FIT**
- **2016.3월** FIT 검사에서 **negative**
- **2016.11월 혈변**으로 내원 => **대장내시경** 검사에서 **대장암 진단**

CS interval cancer

FIT screen-detected cancer

FIT interval cancer

CS interval cancer

- 67세 남자.
- **2015년 대장내시경검사**에서 정상
  => 5년 후 CS f-u 권고 받음.
- **2017년 rectal bleeding**으로 내원
  => **대장내시경검사**에서 **Rectosigmoid colon ca. 진단**.

1
2
3

FIT screen-detected cancer

FIT interval cancer

CS interval cancer ???

- 75세 남자.
- 2013년 대장내시경검사에서 4개의 adenomatous polylp => 3년 후 대장내시경 f-u 권고 받음.
- 2015년 M.I => PCI 시행 후 대장내시경 받지 못함.
- 2017년 rectal blood loss => **대장내시경 검사**에서 **상행결장암 진단됨.**

목차

❖ Detection of CRCs

: Prevalence & Screening

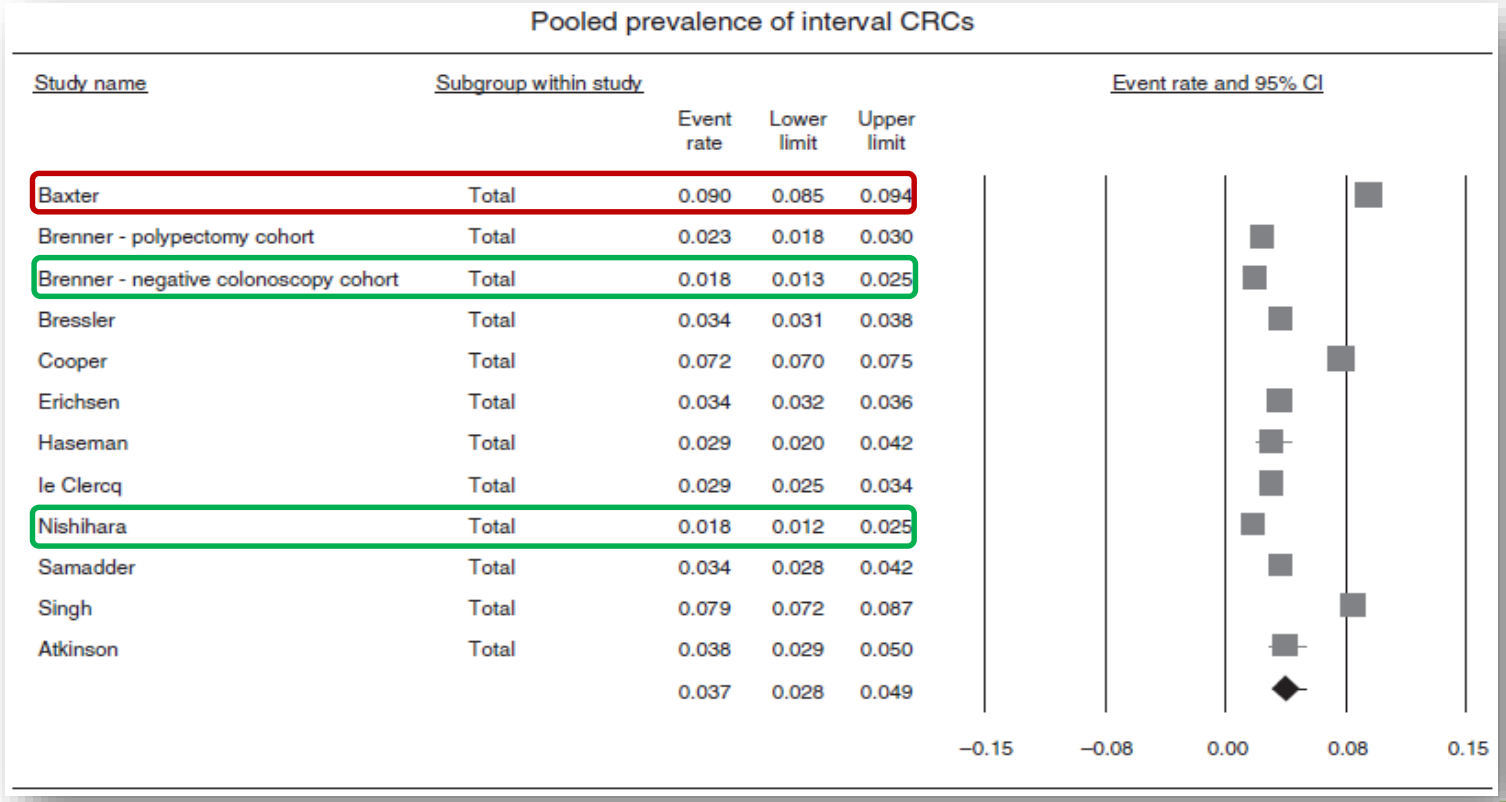
❖ **Interval colon cancer**

- Definition & Taxonomy
- **Prevalence & Risk & Outcome**
- Characteristics
- Cause
- Prevention

Prevalence of interval CRC = **1.8 ~ 9.0 %**

On pooled analysis, the prevalence of interval CRCs

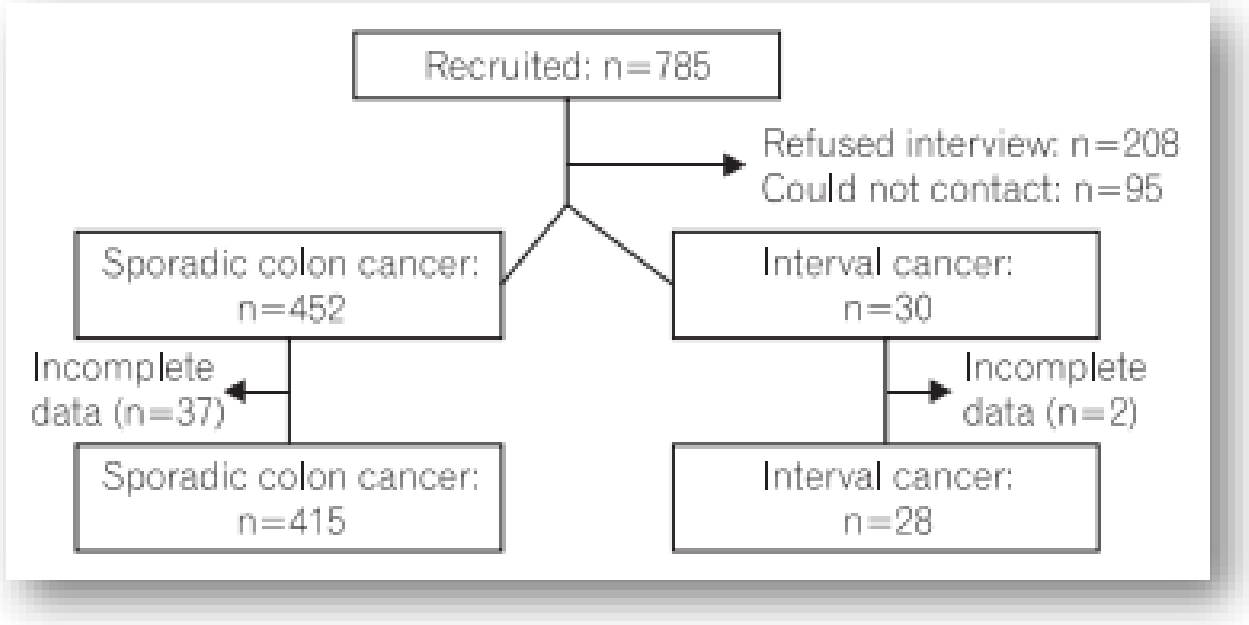
= **4.3 %** (95 % CI = 2.6-6.9 %) within 6~60 months



Am J Gastroenterol 2014; 109:1375–1389

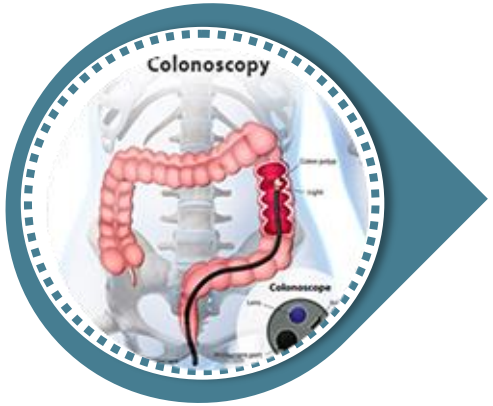
Prevalence of interval CRC in KOREA = 6.2 %

2007~2012. Retrospective, 3RD Referral center
Telephone interview



Intest Res 2013;11(3):178-183

Clinical factor



Endoscopy-related factor

Biology-related factor

Am J Gastroenterol 2014; 109:1375–1389

<<Clinical factor>>

① **Old age** : > 65~70yr vs. < 65~70yr

(OR = 1.12, 95% CI: 1.02–1.30)

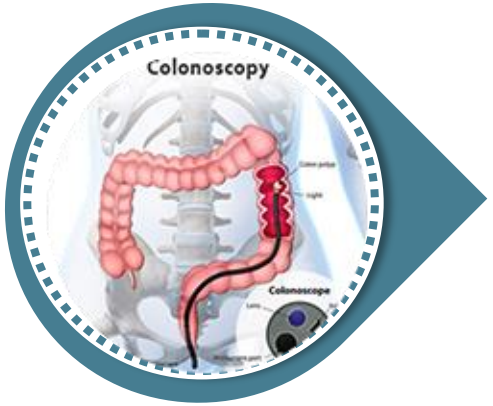
② **Family Hx.** : 1.6배 (OR = 1.64, 95% CI: 1.40–1.90)

③ **Multiple Comorbidity** : 2배 (OR = 2.0, 95% CI: 1.77–2.27)

④ **Diverticular Ds.** : 4.3배 (OR = 4.25, 95% CI: 2.58–7.00)

⑤ **Polypectomy at Index CS** : 1.6배 (OR = 1.57, 95% CI: 0.97–2.56)

Am J Gastroenterol 2014; 109:1375–1389



<<Endoscopy-related factor>>

① Non-gastroenterologist (internist/F.M) vs. Gastroenterologist

OR = 1.53, 95% CI: 1.32–1 .77

Surgeon vs. Gastroenterologist

OR = 1.15, 95% CI: 0.96–1.49

② procedure completion rates and polypectomy rate

OR = 0.70, 95 %CI = 0.63 – 0.77

검사자의 숙련도

최소 400예 이상의 경험

매년 200예의 검사 시행

Am J Gastroenterol 2014; 109:1375–1389

<<Biology-related factor>>

① **CpG island methylator phenotype**

(CIMP; OR = 2.19, 95 % CI: 1.14–4.21)

② **microsatellite instability**

(MSI; OR = 2.10, 95 % CI = 1.10 – 4.02)

Am J Gastroenterol 2014; 109:1375–1389

Stage and grade of CRCs

- ✓ interval CRCs were <u>less likely</u> to be diagnosed at an advanced stage (stage III or IV; OR = 0.79)
- ✓ interval CRCs were just as <u>likely</u> as detected CRCs to be well- to moderately differentiated (G1 / G2: OR = 0.87)

Survival of interval CRCs

As compared with detected CRCs, interval CRCs <u>did not show</u> differences in 5-year survival of patients.

Am J Gastroenterol 2014; 109:1375–1389

목차

1

① Proximal colon >> Distal colon (OR 3.92, 95% CI 2.7-5.6)

② Flat appearance (OR 1.70, 95% CI 1.1-2.4)

③ Small sized (OR 0.78, 95% CI 0.7-0.8)

Table 3 Multiple logistic regression analysis adjusting for age and gender to examine risk factors for postcolonoscopy colorectal cancers (PCCRC)

Postcolonoscopy vs prevalent CRCs*	OR	95% CI	p Value
Proximal location (vs distal)	3.92	2.71 to 5.69	<0.001
Size in cm (continuous)	0.78	0.70 to 0.87	<0.001
Flat appearance (vs protruded)	1.70	1.18 to 2.43	0.004
≥50% mucinous histology (vs <50%)	1.61	0.94 to 2.76	0.085
Specialty of endoscopist (gastroenterologist vs non-gastroenterologist)	1.33	0.81 to 2.19	0.266
Hospital setting (university vs non-university hospital)	1.22	0.82 to 1.83	0.333

*Adjusted for age and gender.
CRC, colorectal cancer.

Gut 2014;63:957–963.

1

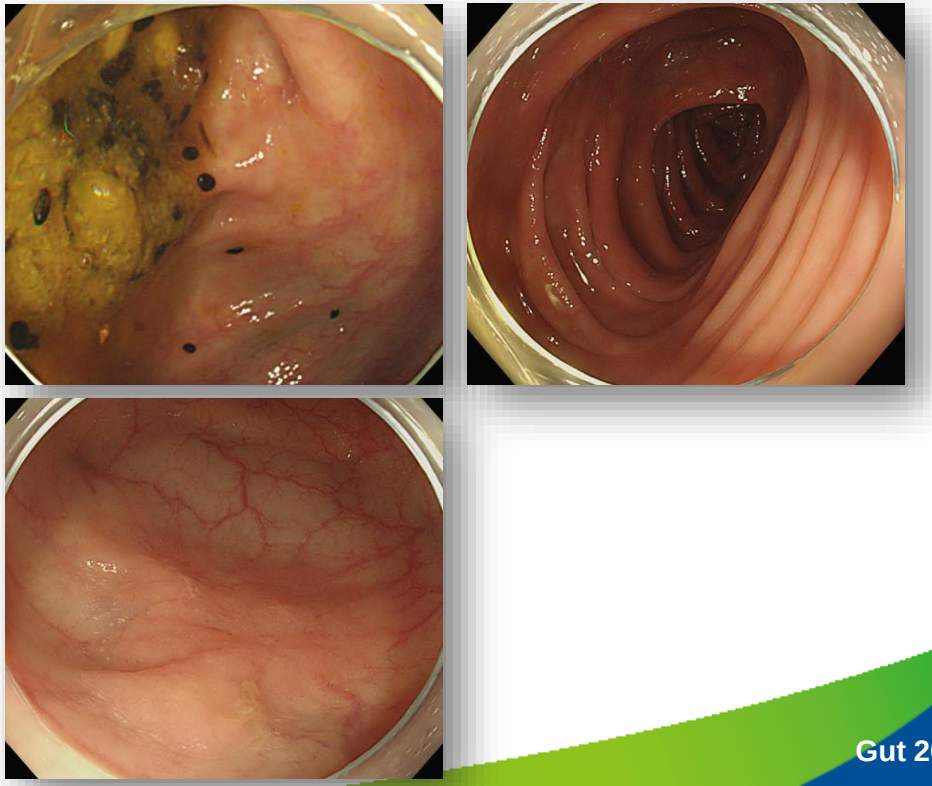
① Proximal colon >> Distal colon (OR 3.92, 95% CI 2.7-5.6)

② Flat appearance (OR 1.70, 95% CI 1.1-2.4)

③ Small sized (OR 0.78, 95% CI 0.7-0.8)

Proximal colon

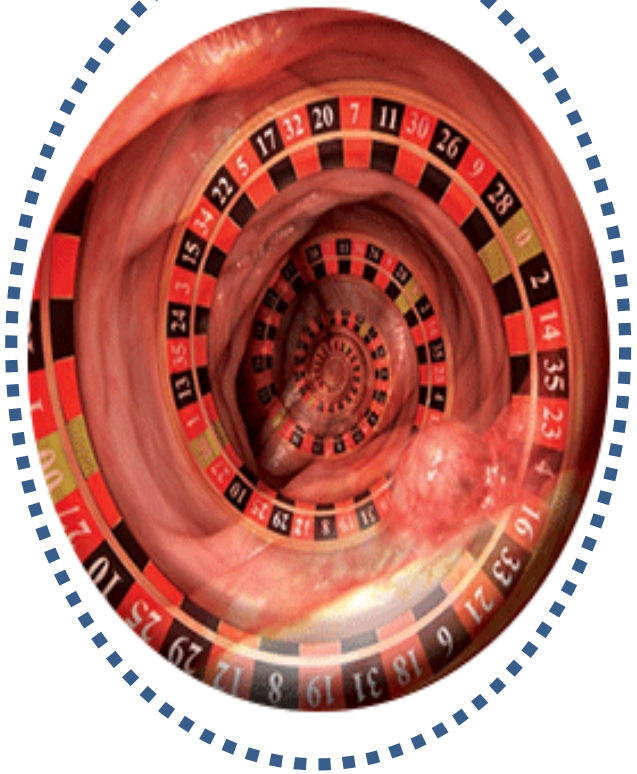
- Worse bowel preparation
- More incomplete colonoscopies
- More difficult to examine
- Flat lesions



Gut 2014;63:957–963.

목차

missed lesion

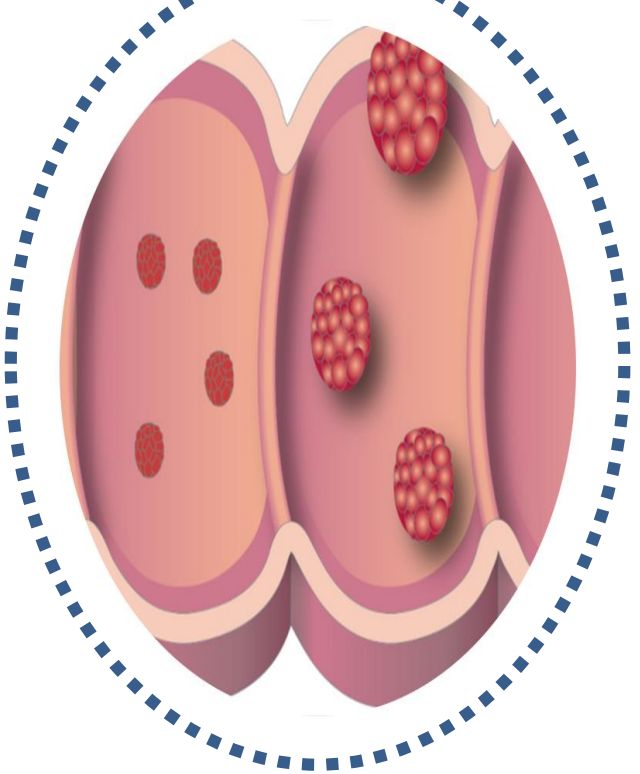


52%

Incomplete Rx.

19%

New lesions

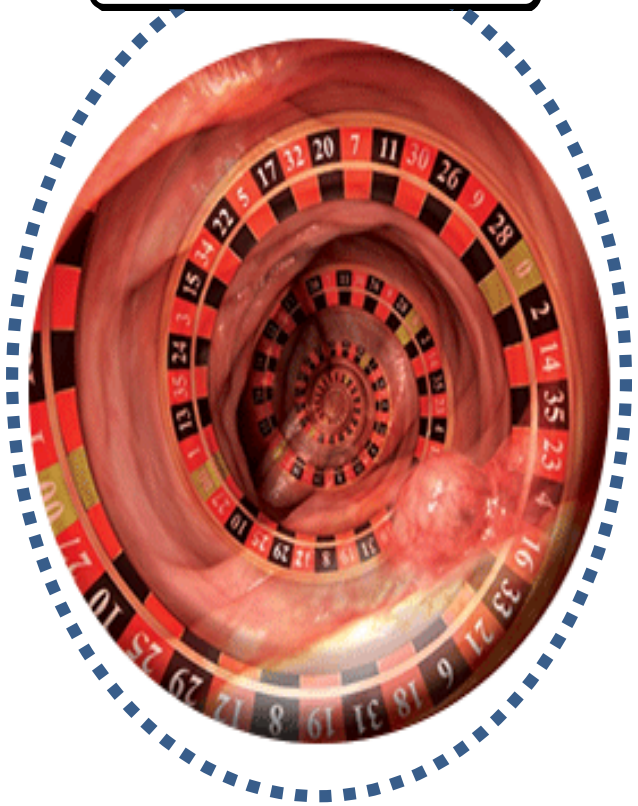


24%

Gut. 2014 Jun; 63(6): 949–956.

V. Cause - missed lesion

missed lesion



52%

Miss rate (overall = 21%)

: Adenomas = 20-24%, Polyps = 22-28%

① **Size**

1~5mm = 26%

5~9mm = 13%,

≥ 10mm = 2%

② **Morphology** : Flat / Sessile

③ **Total number** : ≥ 3

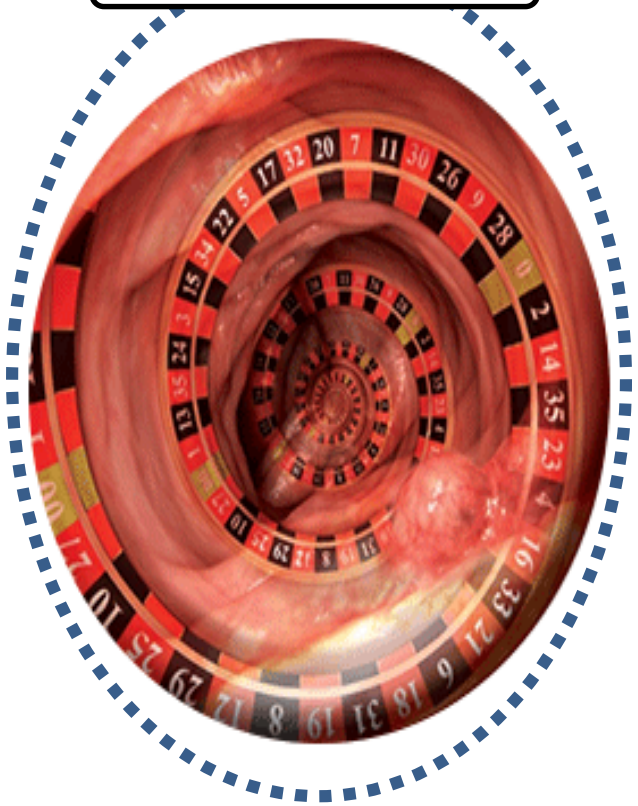
④ **Poor Bowel prep.**

Am J Gastroenterol. 2006 Feb;101(2):343-50.
Endoscopy. 2004 Jun;36(6):499-503.
Endoscopy. 2008 Apr;40(4):284-90.

V. Cause - missed lesion

1
2
3

missed lesion



52%

① Withdrawl time

	6분 미만	6분 이상
ADR	11.8 ± 2.2	28.3 ± 4.0
Advanced neoplasia	2.6 ± 1.1	6.4 ± 1.7

② Suboptimal observation techniques

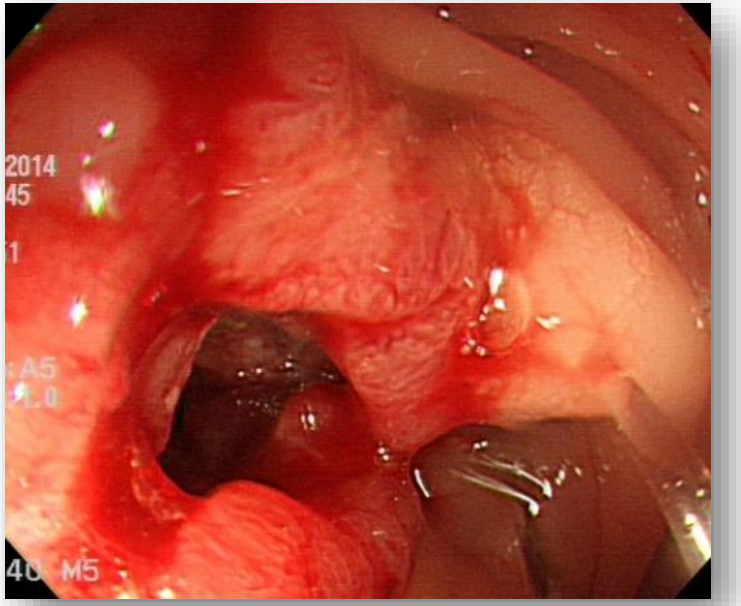
: Adquate cleansing, Adequate distension,

Looking on prox. side of folds

Adequate of time spent wiew

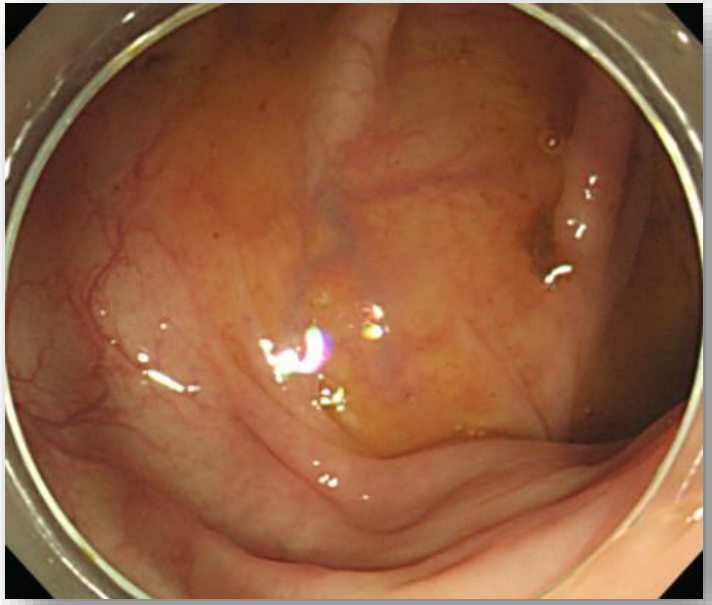
N Engl J Med 2006; 355:2533-2541
Clin Endosc. 2012 Nov; 45(4): 404–411.

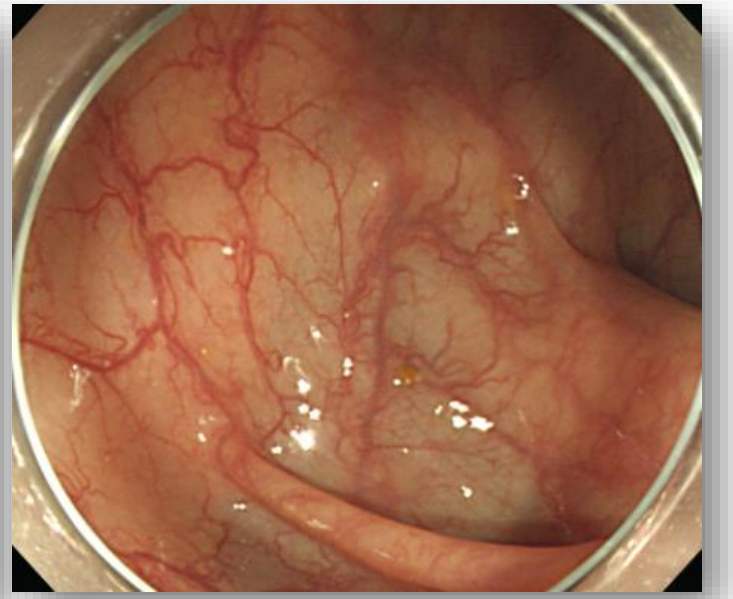
Case - missed lesion



2014 Descending colon ca.

=> Lt. hemicolectomy





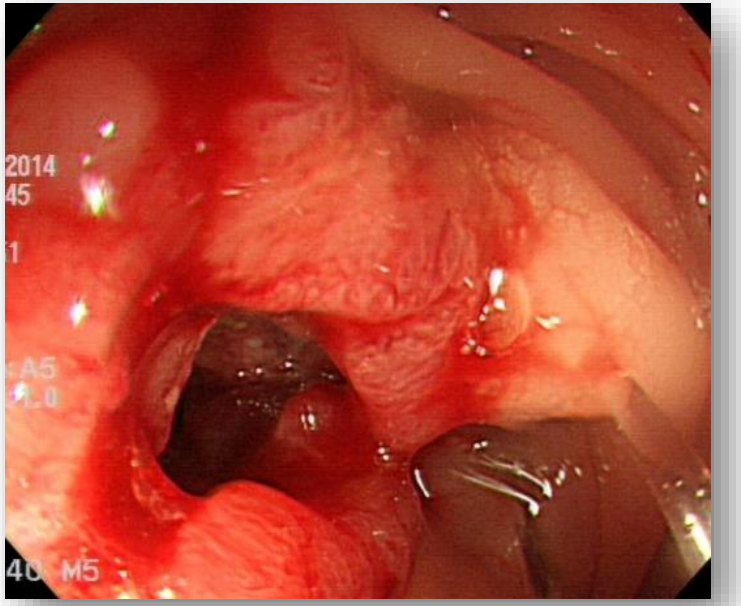
2016 f-u Colonoscopy

: Post OP colon

(s/p Lt. hemicolectomy

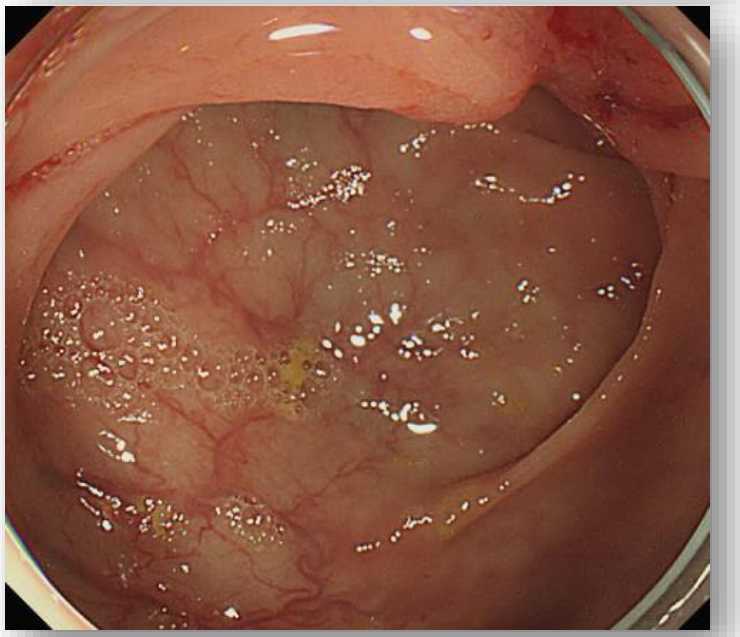
d/t D-Colon ca.)

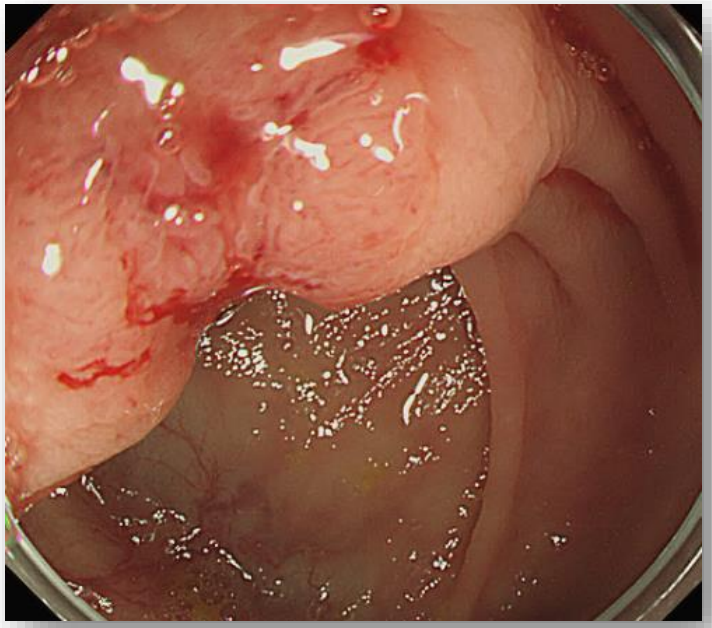
Case - missed lesion



2014 Descending colon ca.

: D-colon ca. Lt. hemicolectomy

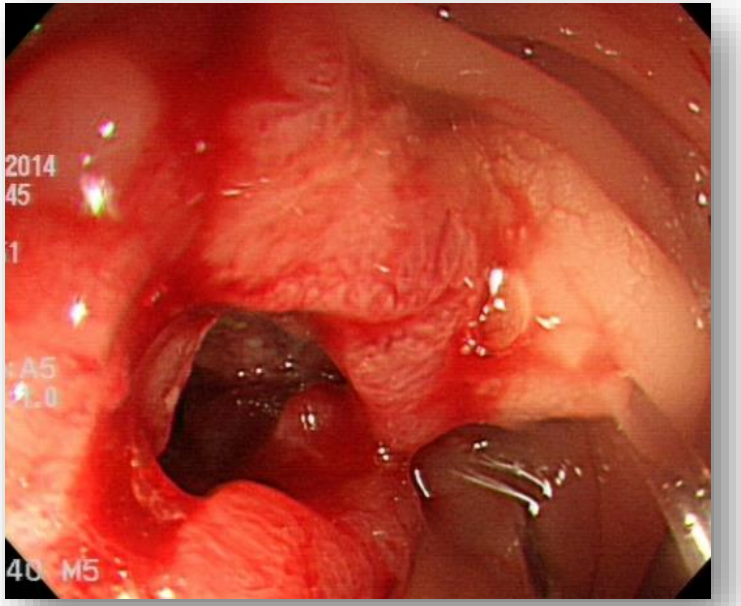




2017 f-u Colonoscopy

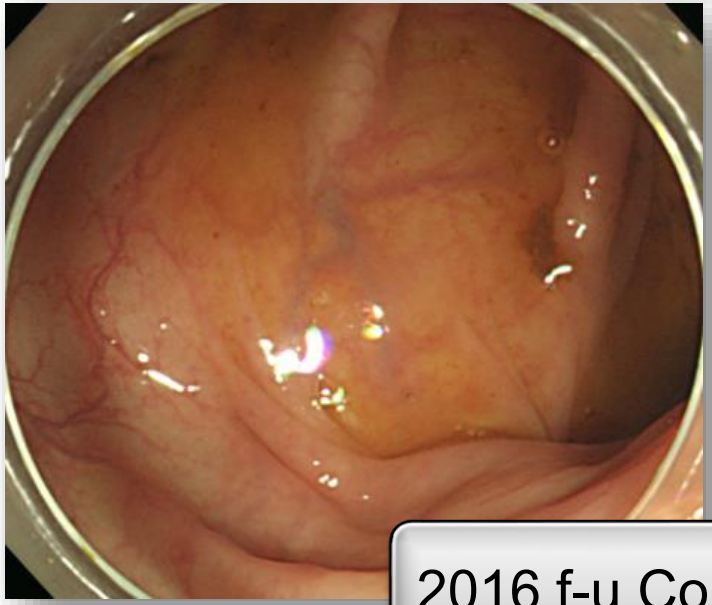
: Interval cancer on HF

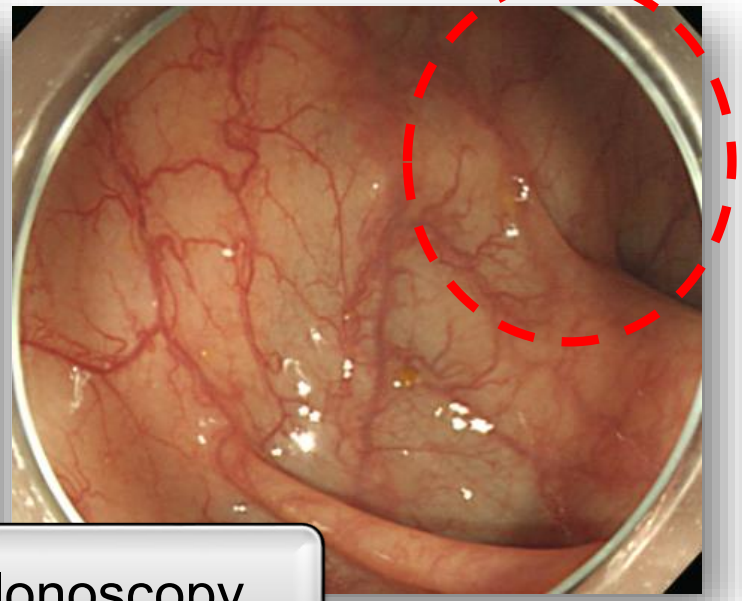
Case - missed lesion



2015 Descending colon ca.

: D-colon ca. Lt. hemicolectomy



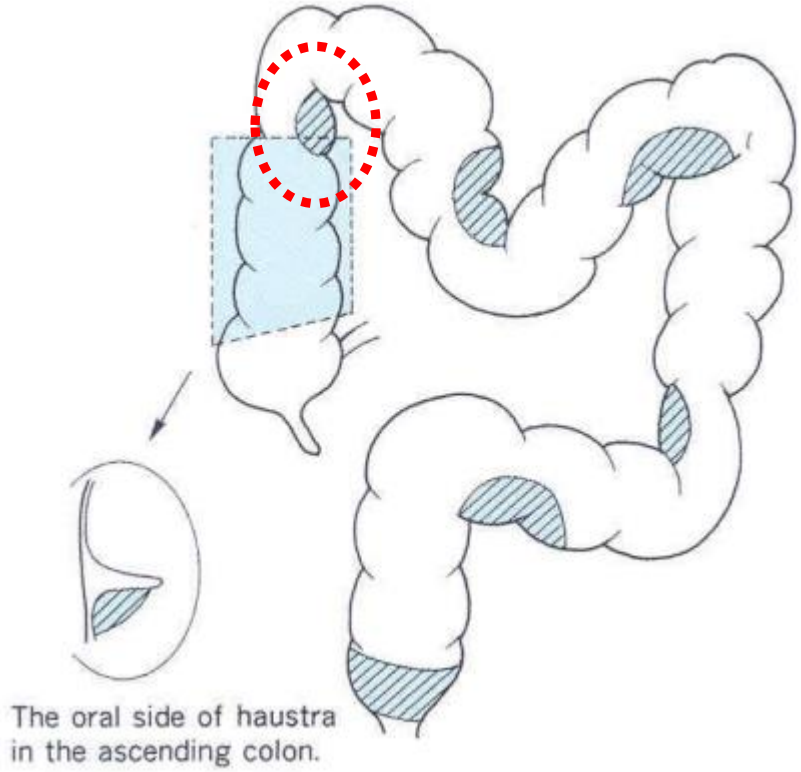


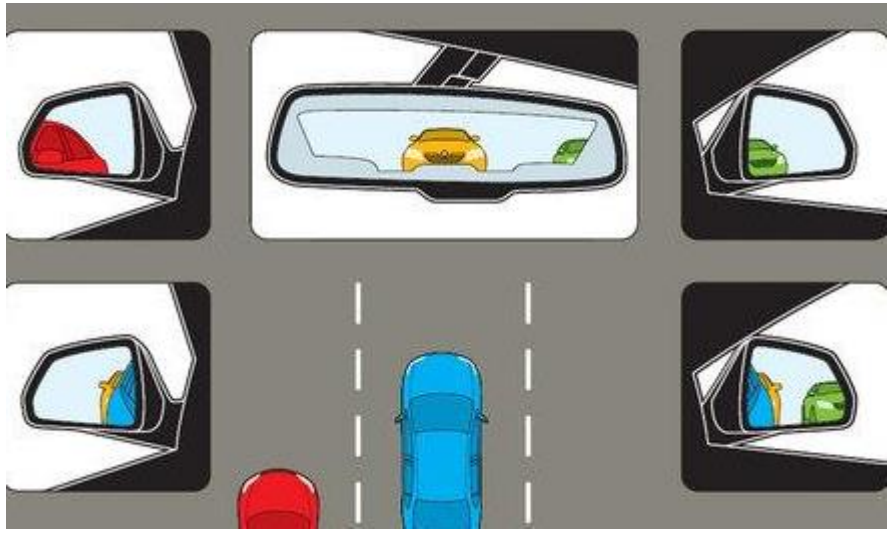
2016 f-u Colonoscopy

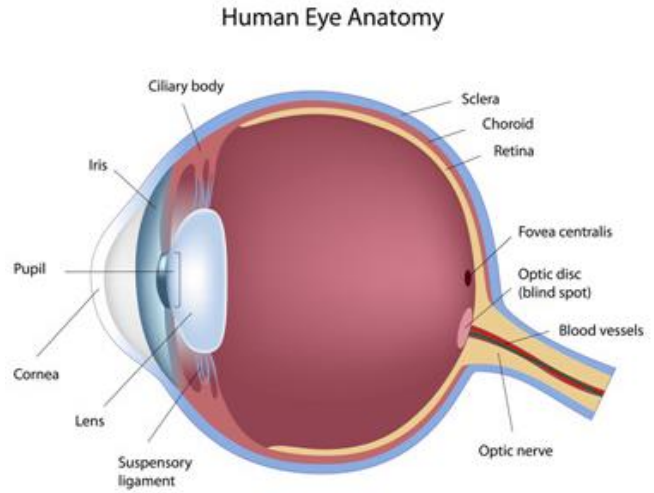
2017 f-u CS

Case - missed lesion

대장내시경 맹점부위

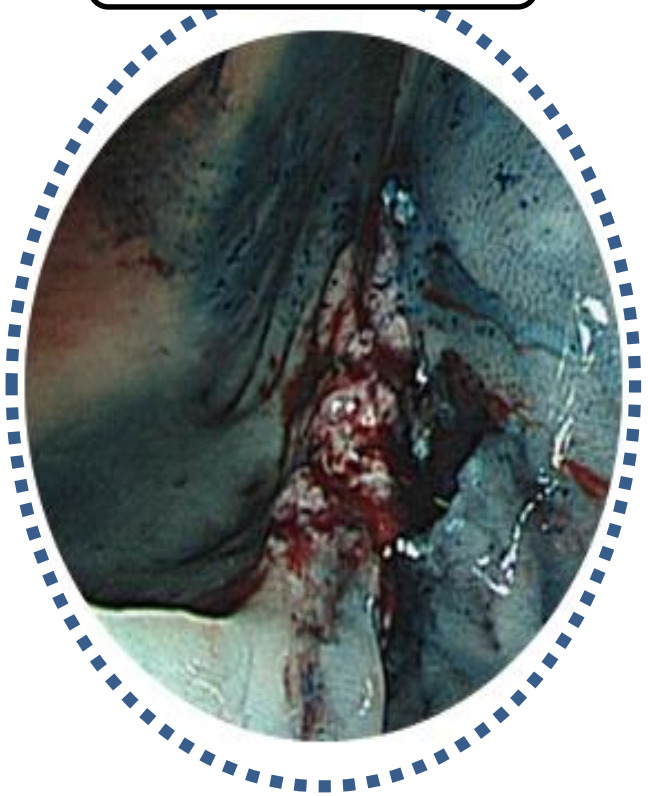






1
2
3

Incomplete Rx.



19%

Result of the Complete Adenoma Resection [CARE] study

Pathologically incomplete resection rate = **10.1%**

① **Size**

: 10-20mm vs. <10mm : 17% vs. 6.8%

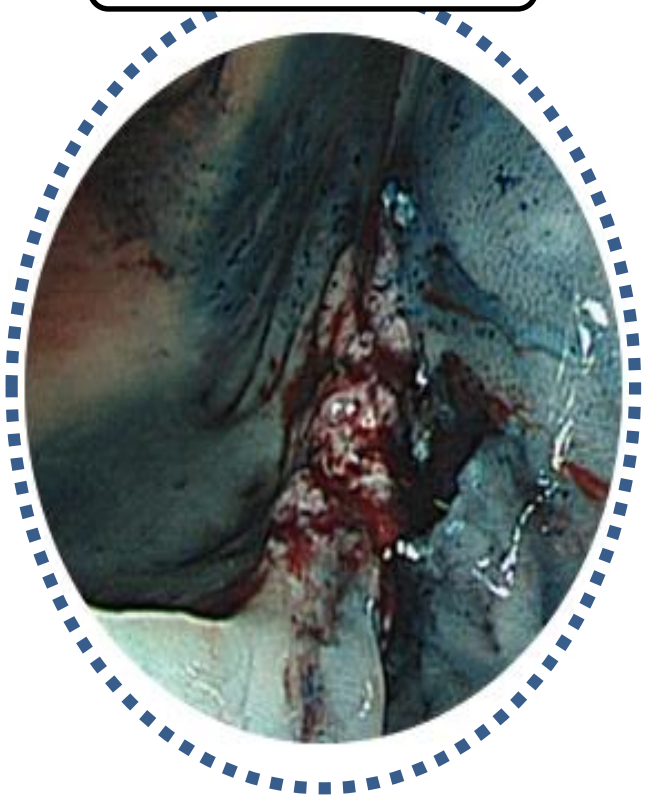
② **Histology**

: SSA/P vs. Adenoma : 31% vs. 7.2%

Gastroenterology. 2013 Jan;144(1):74-80

V. Cause - incomplete Rx.

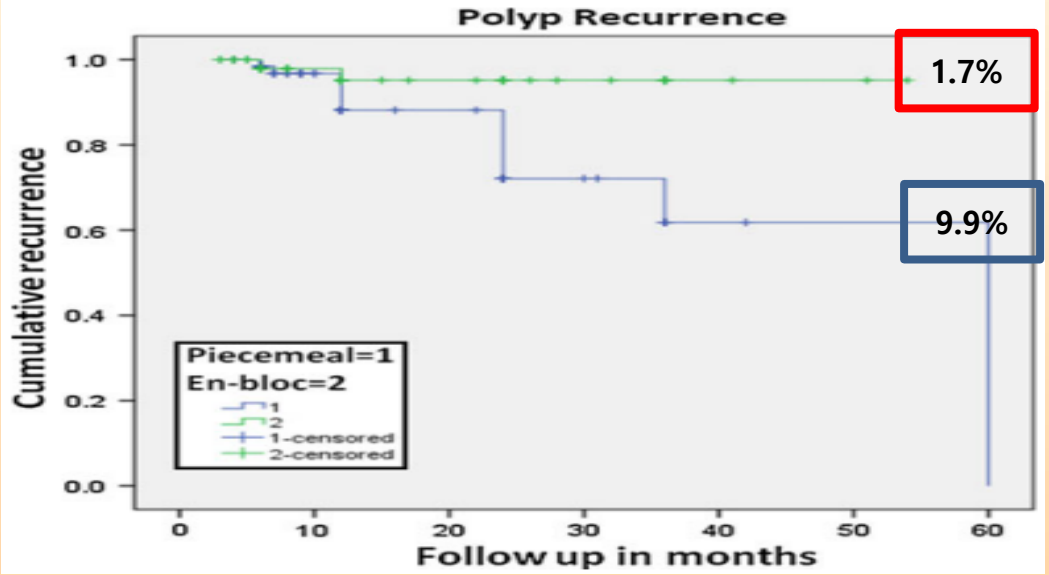
Incomplete Rx.



19%

① Piecemeal Rx. (large sessile polyp ≥ 2cm)

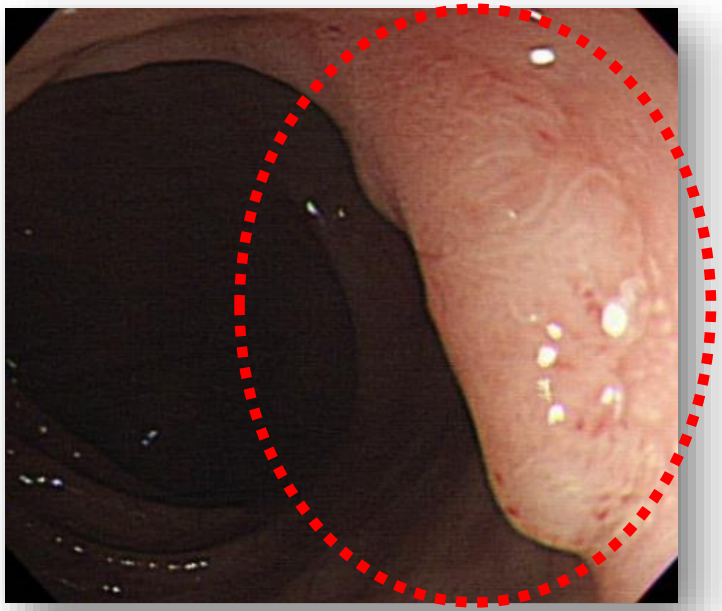
: mean recurrence rate = 25% (0~55%)

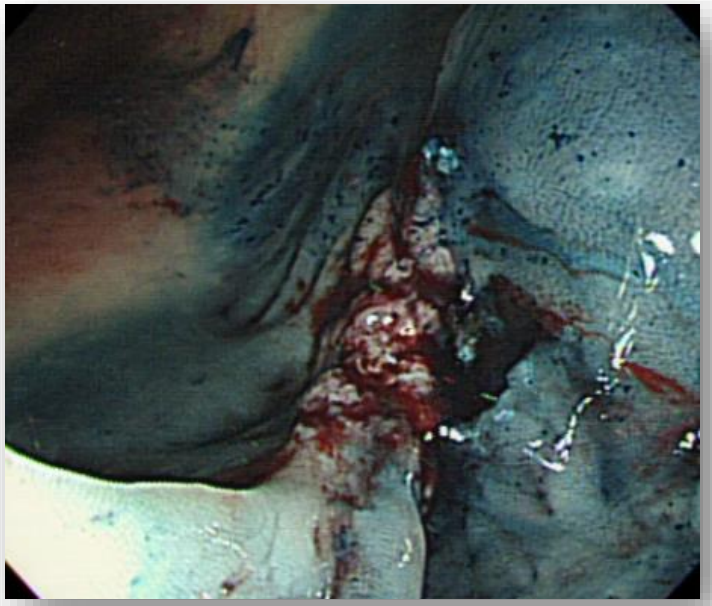


: Endoscopist technique

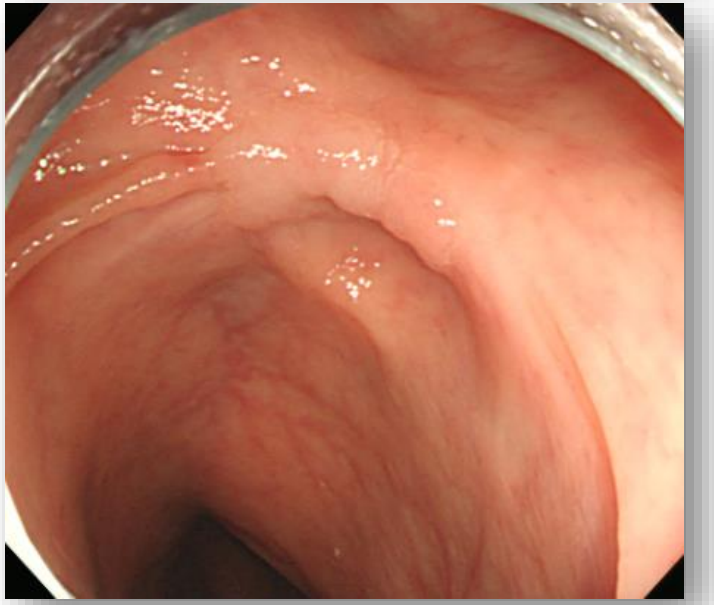
Gastrointest Endosc. 2009 Aug;70(2):344-9.
Dig Dis Sci (2011) 56:2389–2395

Case - incomplete resection ①



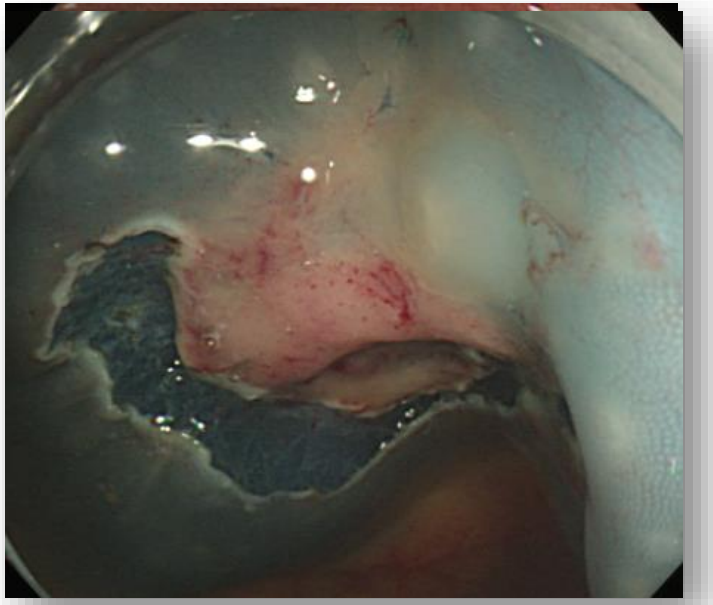


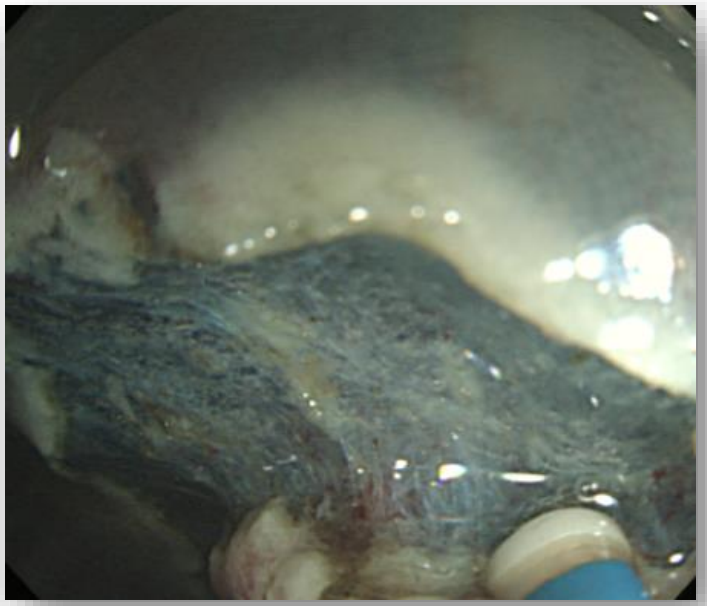
Local H. : LST => incomplete Rx

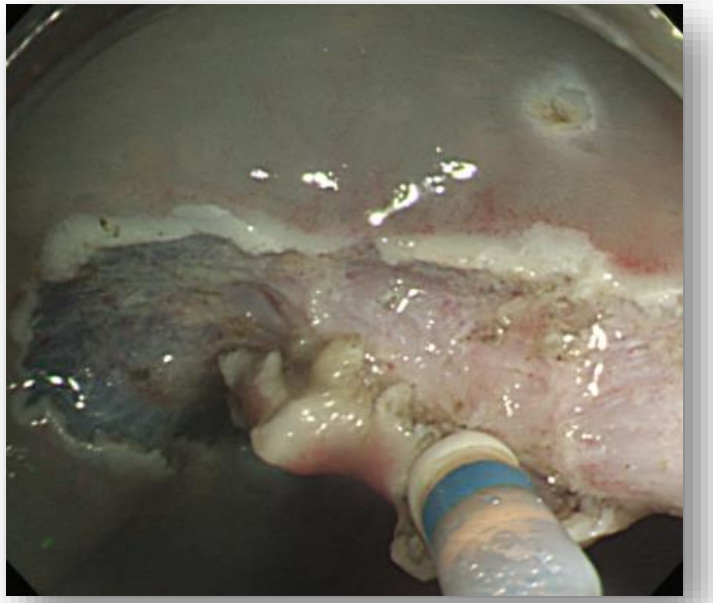


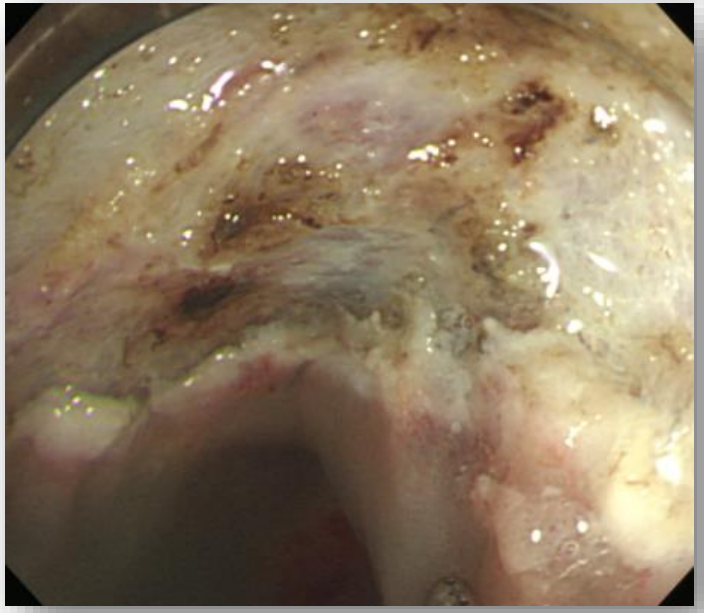
PNUH Referral

Case - incomplete resection ①



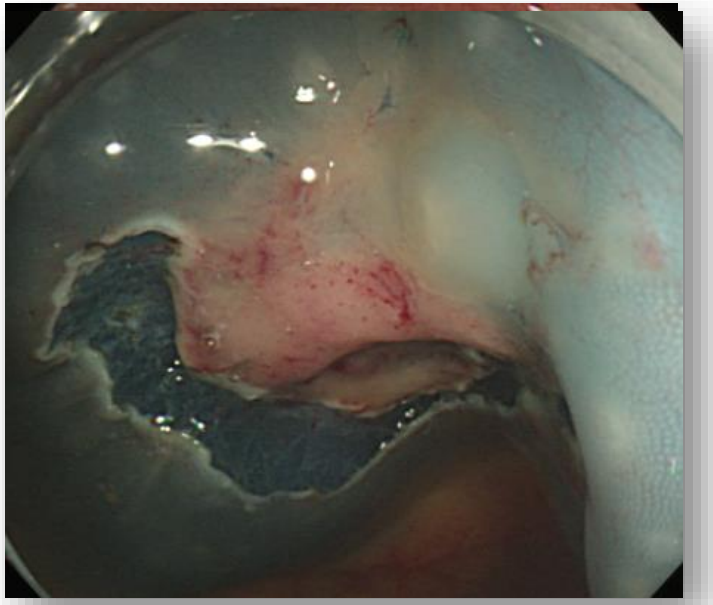


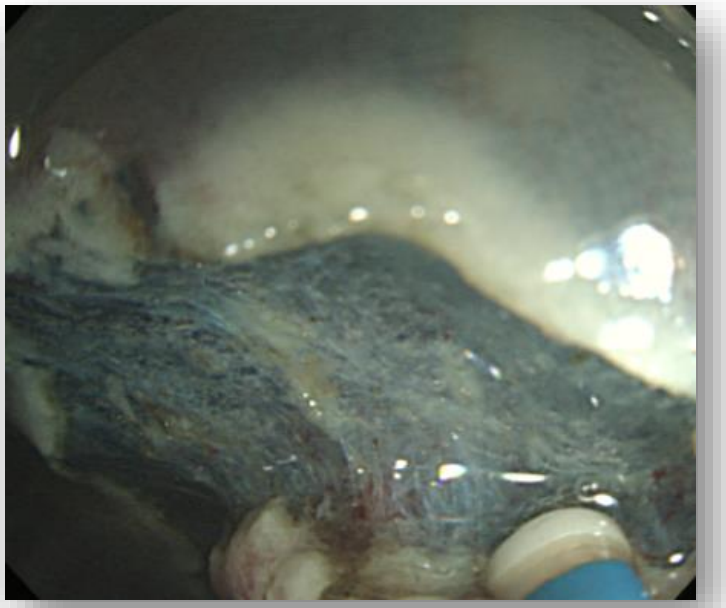


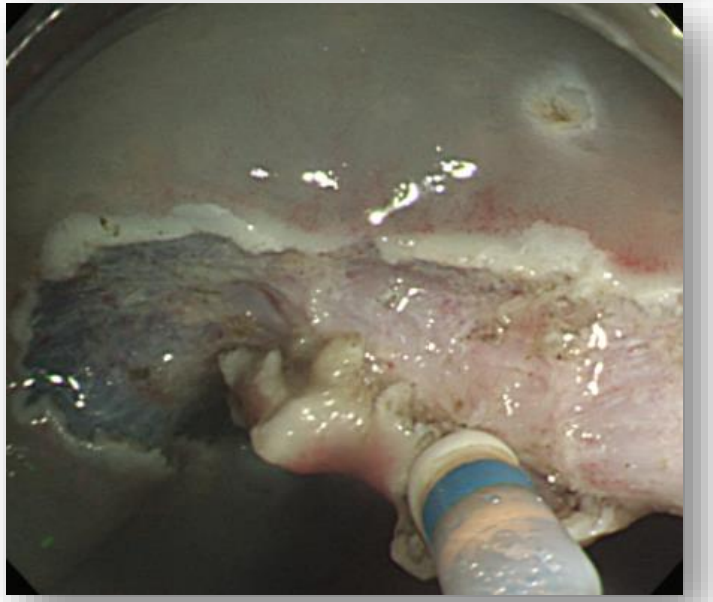


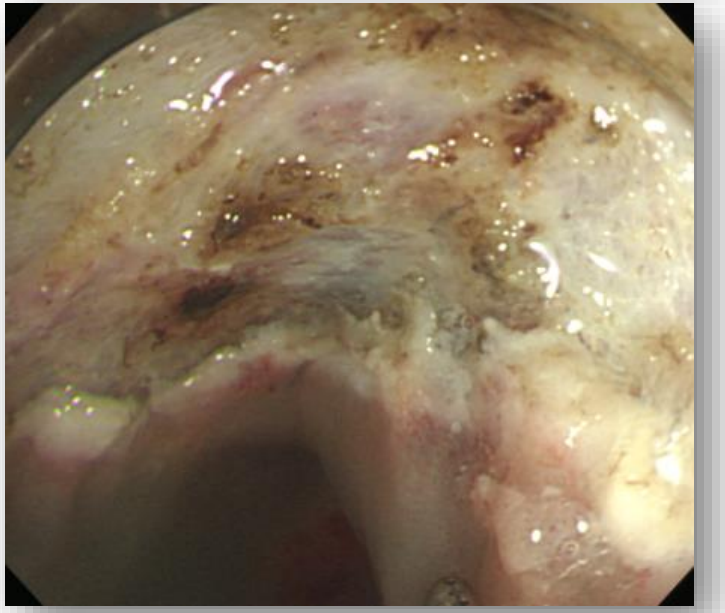
Incomplete resected LST
/c scar change => ESD
: T.A /c LGD

Case - incomplete resection ①

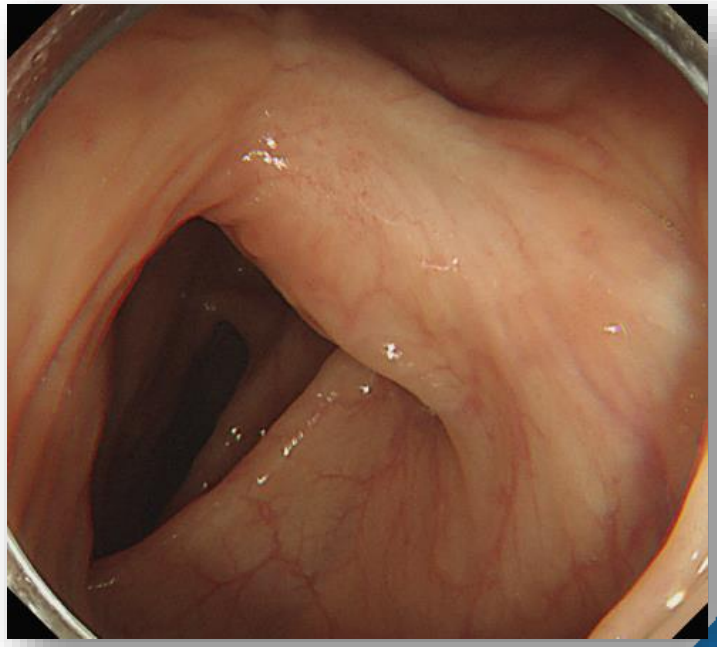




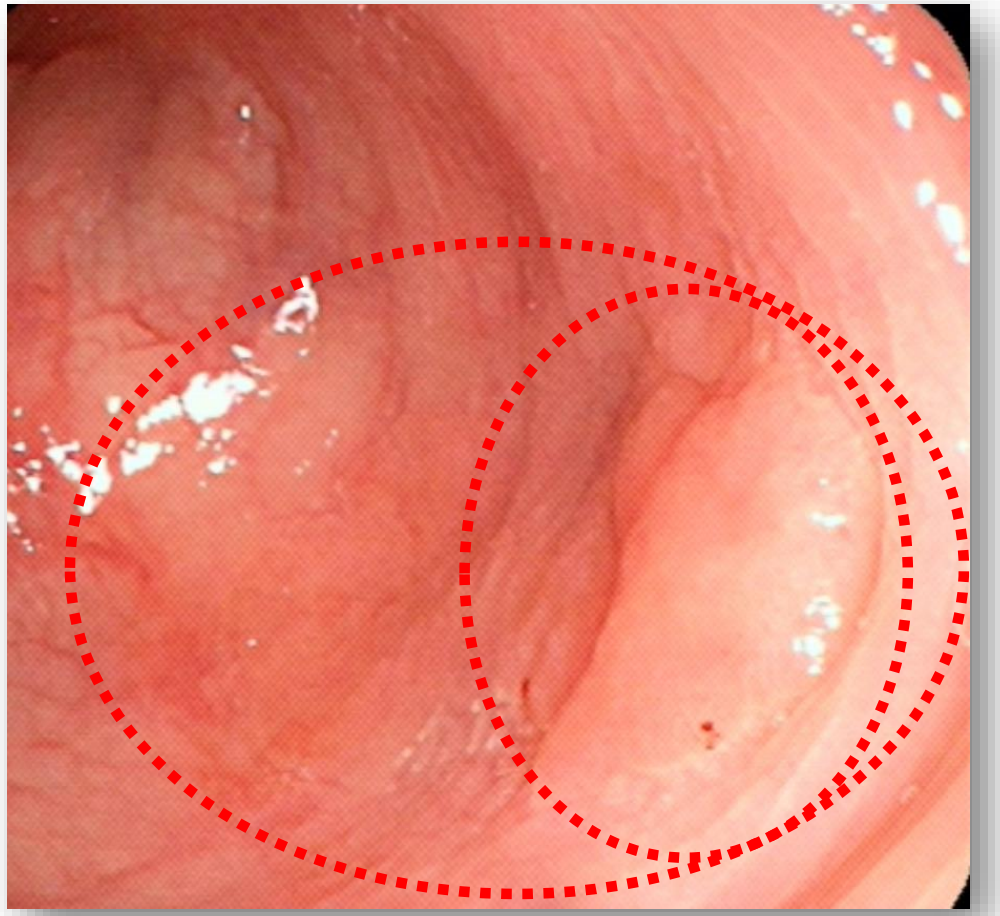




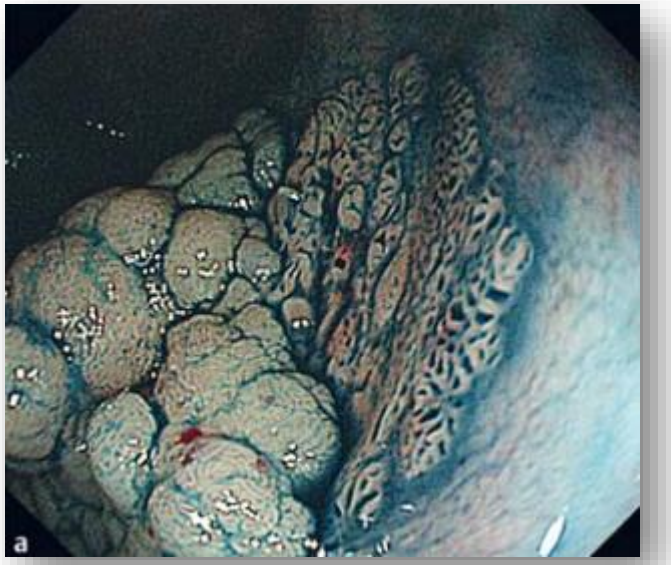
F-U Colonoscopy after 6 month.

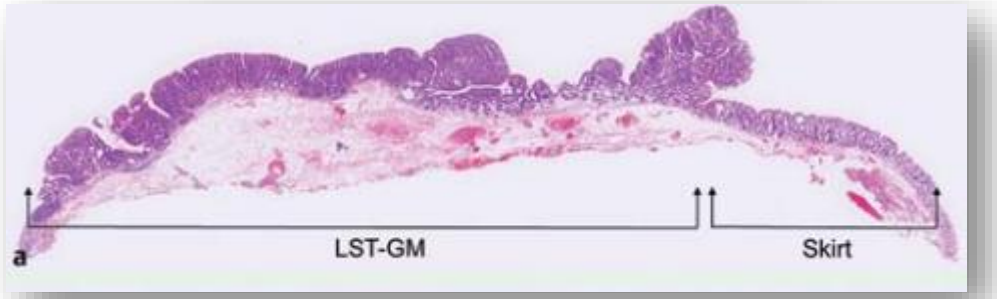


LST의 Margin은 ?



Clinicopathological, endoscopic, and molecular characteristics of the "skirt" – a new entity of lesions at the margin of laterally spreading tumors





(1) Higher rate of ADC

:LST /c skirt : 80% vs. LST /s skirt : 45.4%

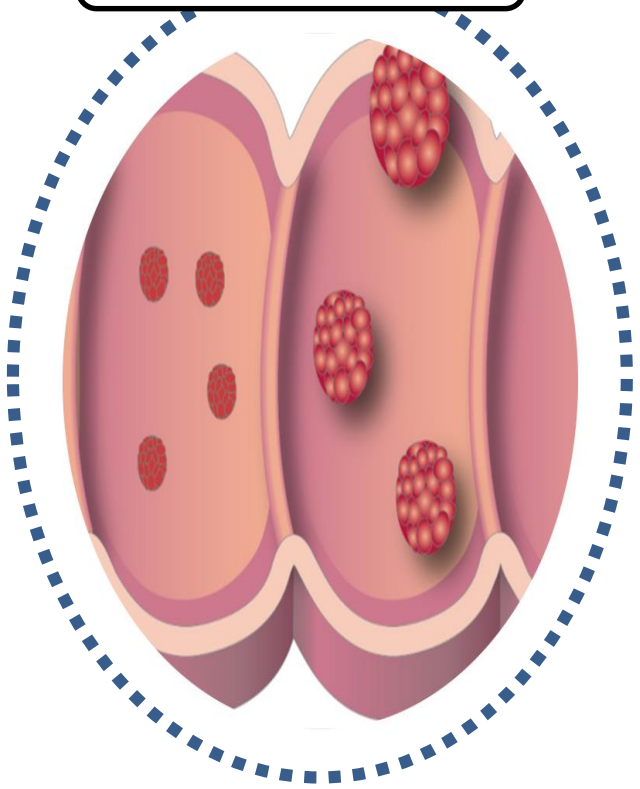
(2) Higher possibility of Incomplete Rx.

:Interval cancer의 원인

Endoscopy 2016; 48: 448–455

V. Cause - new lesions

New lesions



24%

Interval cancer

: Proximal colon / Flat appearance / large sized

=> **Serrated pathway**

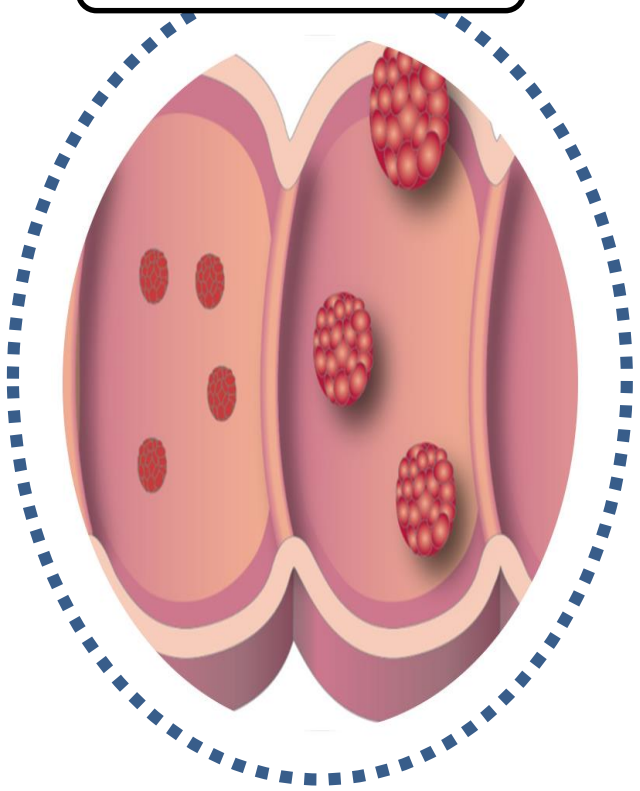
Missed lesion	Incomplete resection
flat, mucous cap	vague margin

Two of following features:

- Clouded surface?
- Indistinctive border?
- Irregular shape?
- Dark spots inside crypts?

AJG 2015 Dec;110(12):1657-64
Gut 2016;65:963–970

New lesions



24%

Molecular feature of the serrated pathway

① **BRAF mutation : 78~90%**

: MAPK pathway activation -> cell prolif. & survival

: MVHP -> Serrated Lesion

② **CIMP (with or without MSI) : 70%**

: loss of suppressor gene <= associated with mBRAF

(MGMT, MLH1, p16, MINT1, MINT2, and MINT31 genes)

❖ DNA mismatch repair (MMR) gene silencing by methylation (**MSI-H, 4배**) / **p53 mutation**

= Rapid progression of serrated polyps to cancers

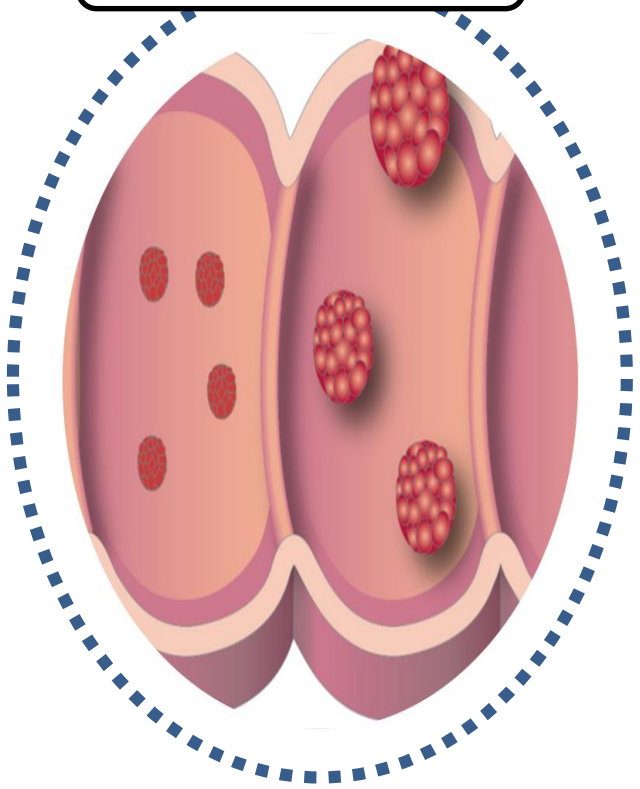
JGH 32 (2017) 358–367

V. Cause - new lesions

부산대학교병원 Pusan National University Hospital

1
2
3

New lesions



24%

Clinicopathological Characteristics of Interval and Sporadic Cancers

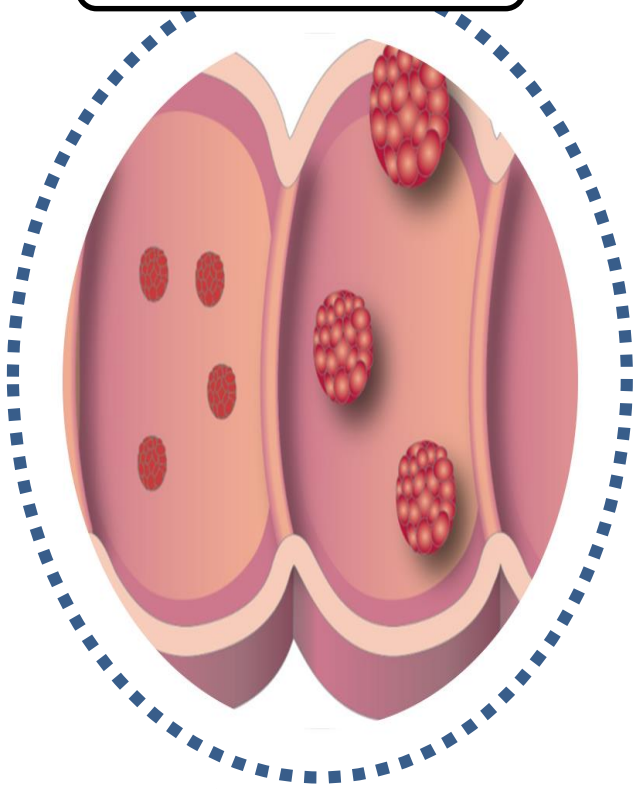
Characteristic	Interval cancer (n=25)	Sporadic cancer (n=261)	p-value
Tumor size, cm	3.8±2.4	4.3±2.0	0.260
Location (proximal)*	13 (52)	77 (29)	0.020
MSI positivity†	8 (32)	22 (8.4)	0.002
TNM stage			0.055
1	9 (36)	55 (21)	
2	8 (32)	72 (27)	
3	6 (24)	101 (38)	
4	2 (8)	33 (12)	
Histologic grade			0.230
Well	3 (13)	14 (5)	
Moderate	19 (86)	232 (91)	
Poor	0	7 (3)	
Mucinous‡	3 (12)	8 (3)	0.060

Gut Liver. 2016 Sep; 10(5): 781–785.

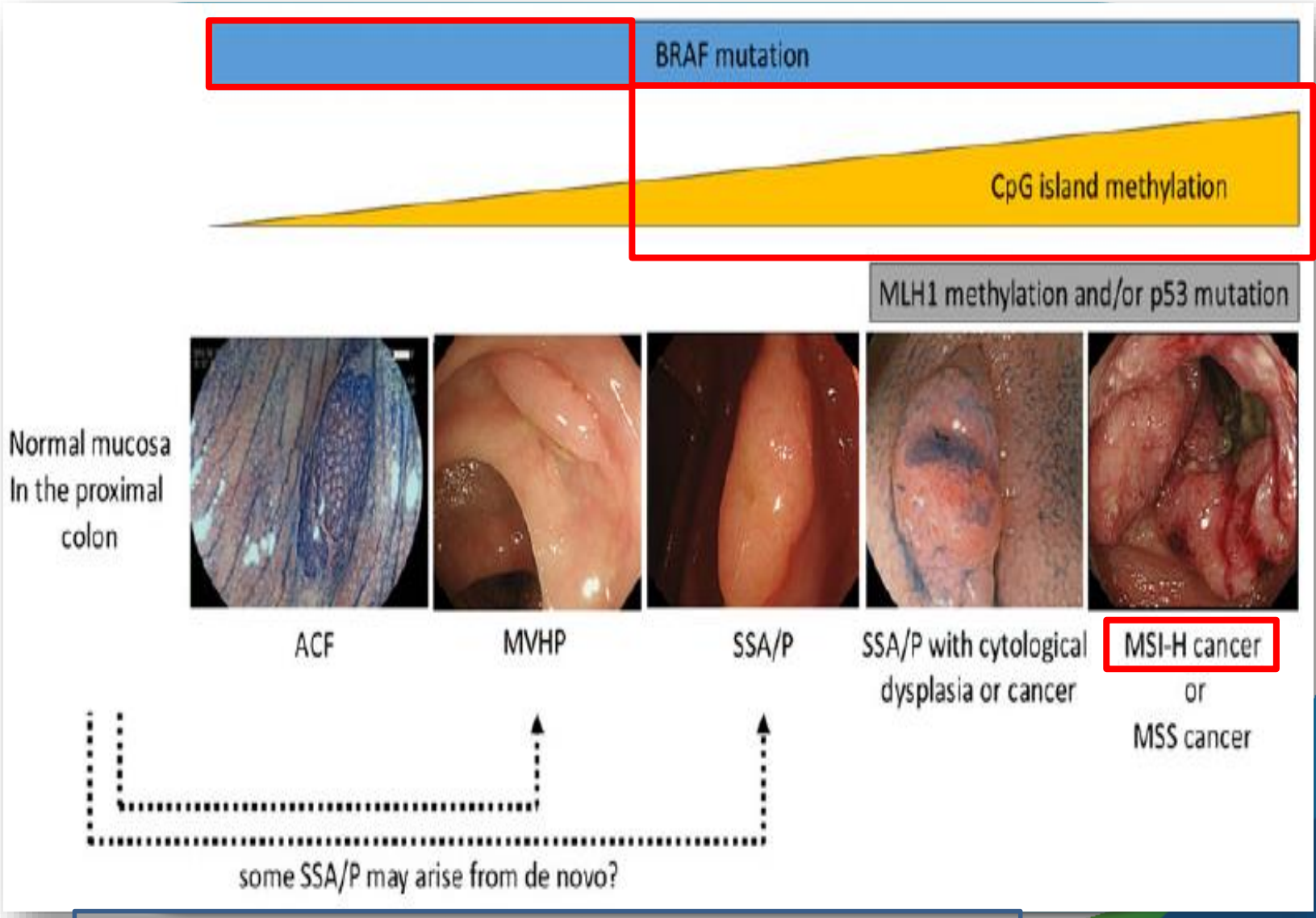
V. Cause - new lesions

1
2
3

New lesions



24%



serration
: increased turn over, delayed migration, suppresed apoptosis

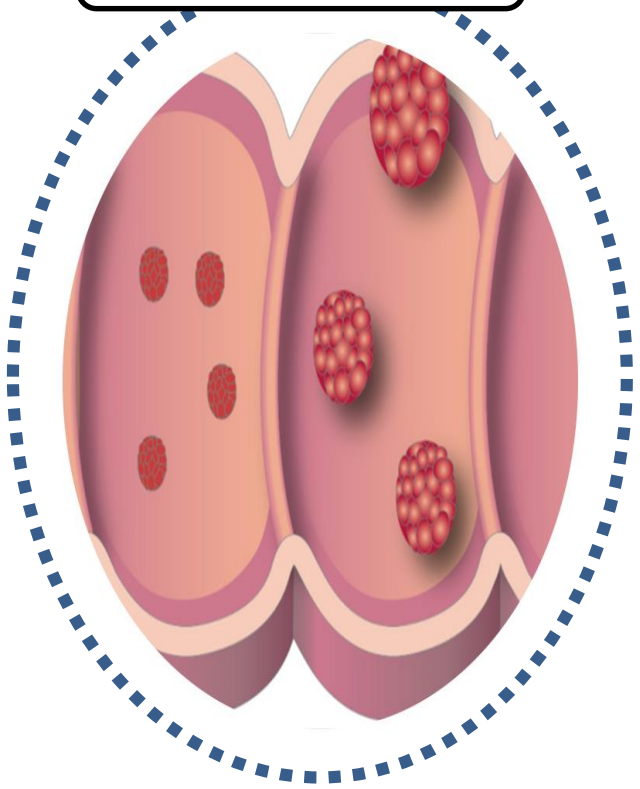
JGH 32 (2017) 358–367

V. Cause - new lesions

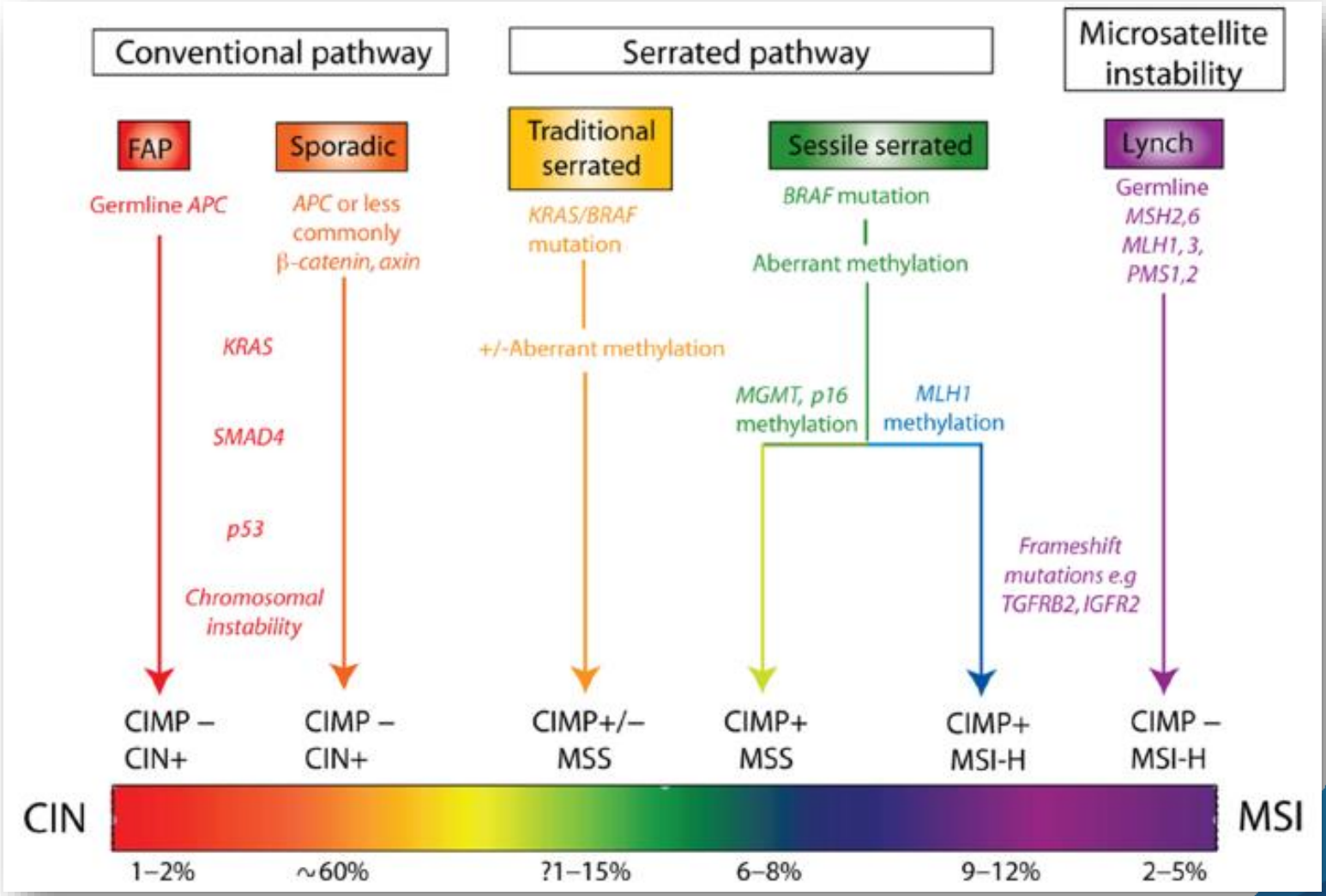
부산대학교병원 Pusan National University Hospital

1
2
3

New lesions



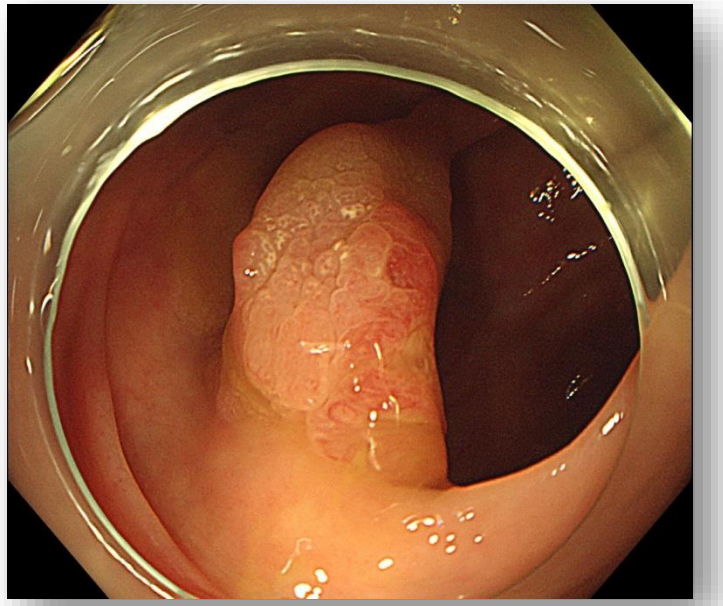
24%

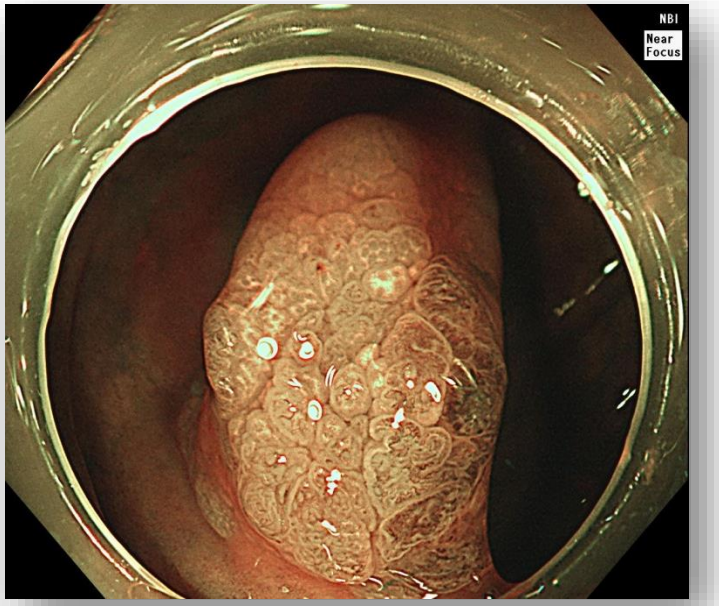


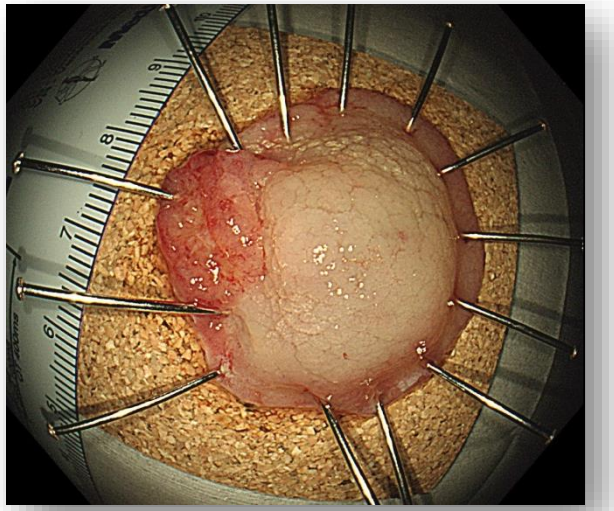
serration
: increased turn over, delayed migration, suppresed apoptosis

Gut 2017;66:1181–1196

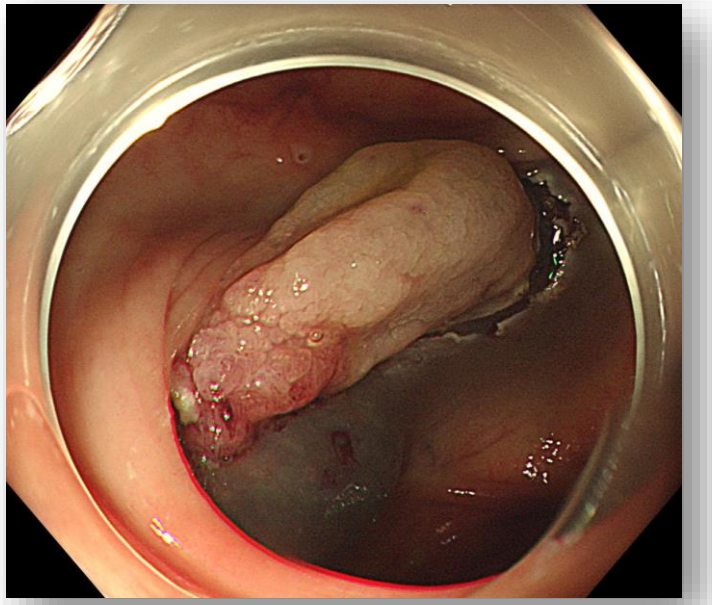
Case - new lesion

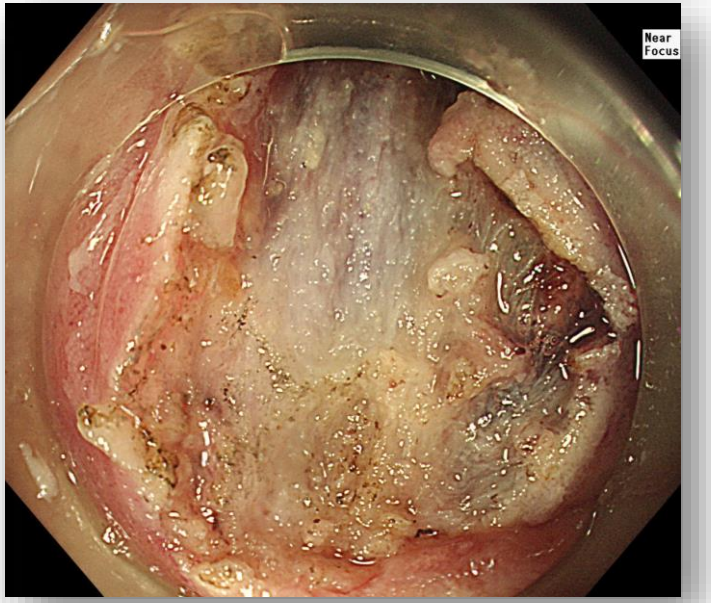


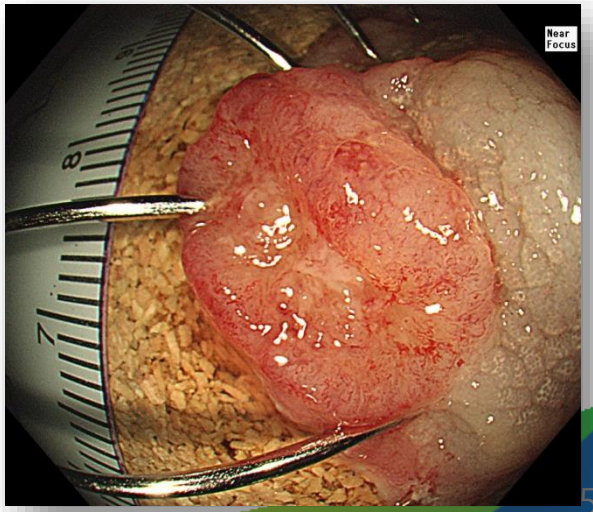




ADC arising from SSA/P

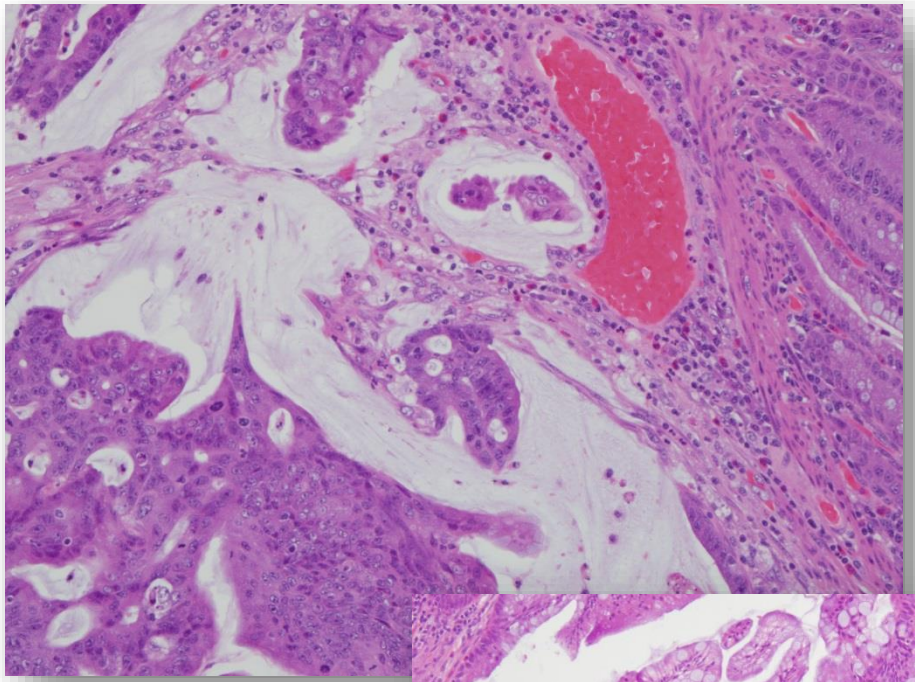


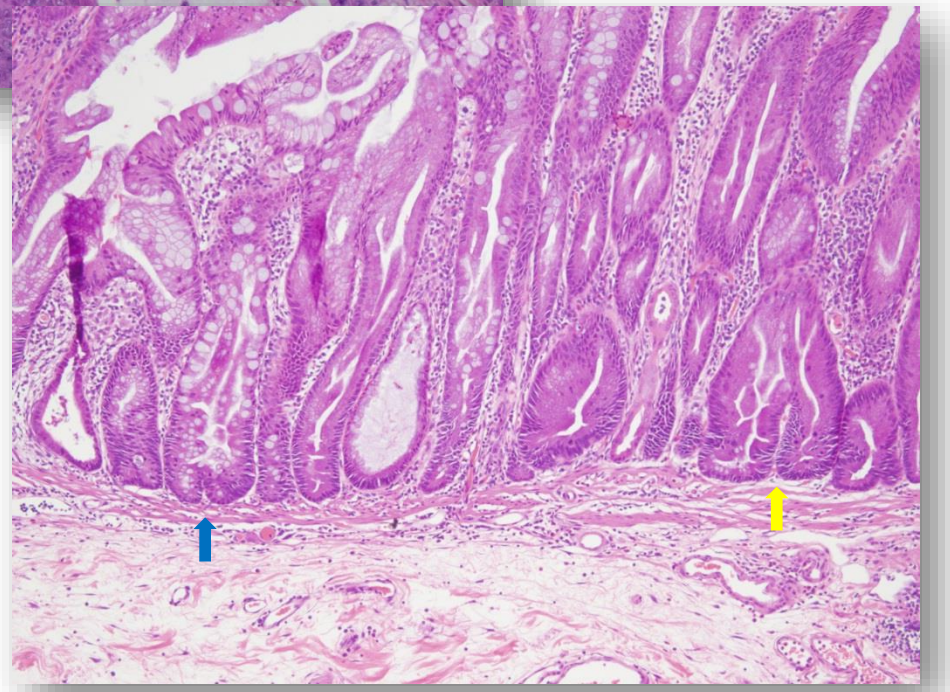




Courtesy of Dr. Kim Hyung Wook

Case - new lesion





Early Colon Cancer : mod. diff. ADC

Size of whole tumor : 1.8x1.7cm

Size of invasive carcinoma : 0.8x0.8cm

Tumor invades submucosa (pT1).

* Depth of invasion : 4000um / 4750um

* Additional Pathologic Findings

- Sessile serrated adenoma with high grade dysplasia.

Courtesy of Dr. Kim Hyung Wook

목차

Failure of colonoscopy to detect colorectal cancer: evaluation of 47 cases in 20 hospitals

GASTROINTESTINAL ENDOSCOPY
VOLUME 45, NO. 6, 1997

Joseph H. Haseman, MD, Gregory T. Lemmel, MD, Emad Y. Rahmani, MD, Douglas K. Rex, MD

Indianapolis, Indiana

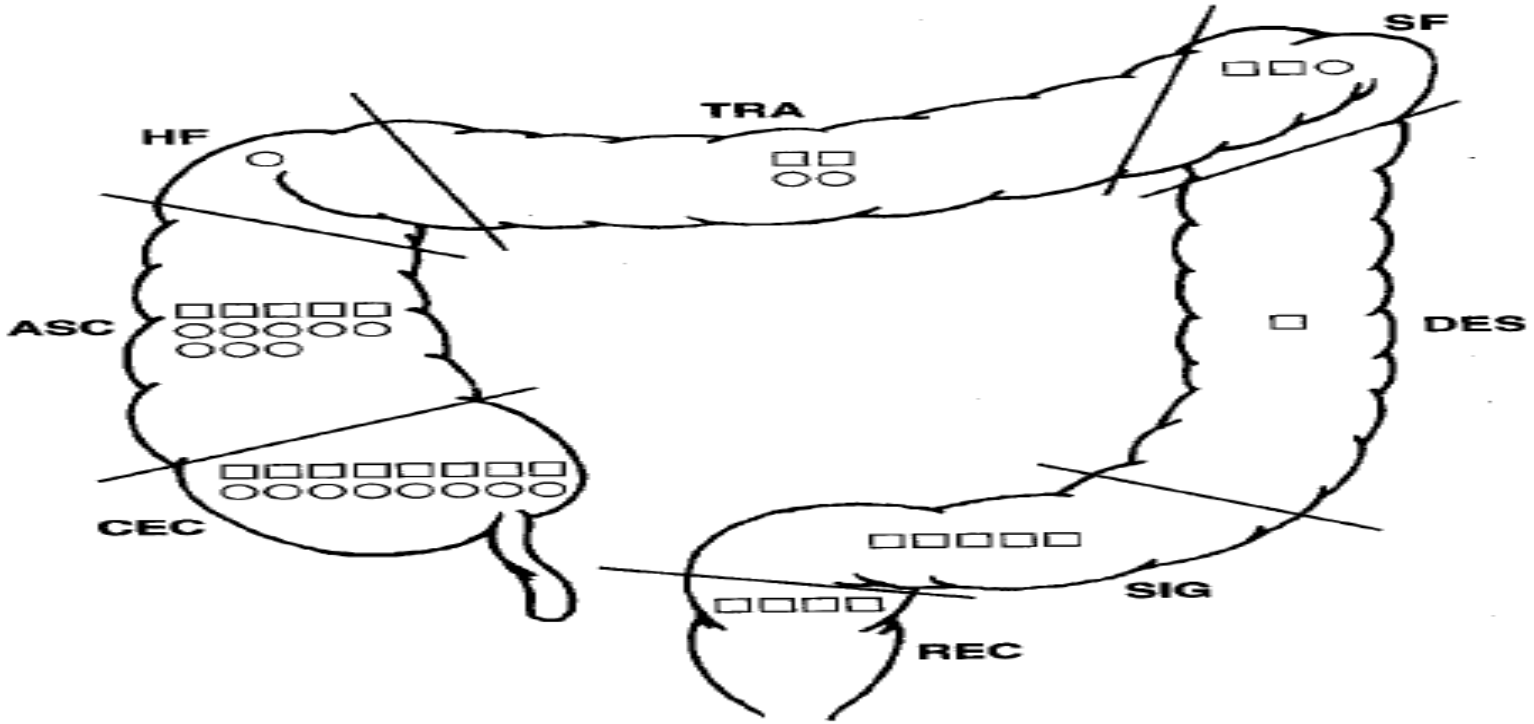
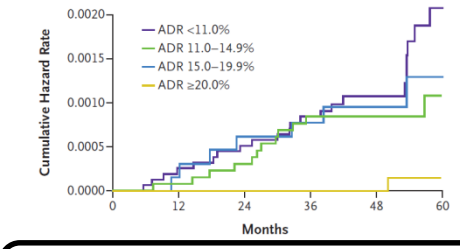


Figure 1. Location of colorectal cancers "missed" (□) and "not reached" (○). *CEC*, Cecum; *ASC*, ascending; *HF*, hepatic flexure; *TRA*, transverse; *SF*, splenic flexure; *DES*, descending; *S*, sigmoid; *REC*, rectum.

1

2

❖ Colonoscopy Quality is the Answer for the Emerging Issue of Interval Cancer !!!



Bowel prep.

Adequate bowel prep.

≥ 85%

고령 / **comorbid condition**

Split dose vs. same day

satisfactory prep : 3.7배
willingness to repeat : 1.8배

Cecal intubation rate

Cecal intubation rate

≥ 90% (*all exam*)

≥ 95% (*screening CS*)

여성(longer/redundant) / 고령
복부 또는 골반 내 수술의 과거력

Reattempt / Referral

지속적인 교육

ADR

Adenoma detection rate

***overall target* ≥ 25%**

≥ 30% *for male*

≥ 20% *for female*

ADR 1% ↑
: CRC incidence 3% ↓
: Mortality 5% ↓

Am J Gastroenterol 2015; 110:1657–1664

부산대학교병원 Pusan National University Hospital

1

2

❖ Follow-up/surveillance recommendations

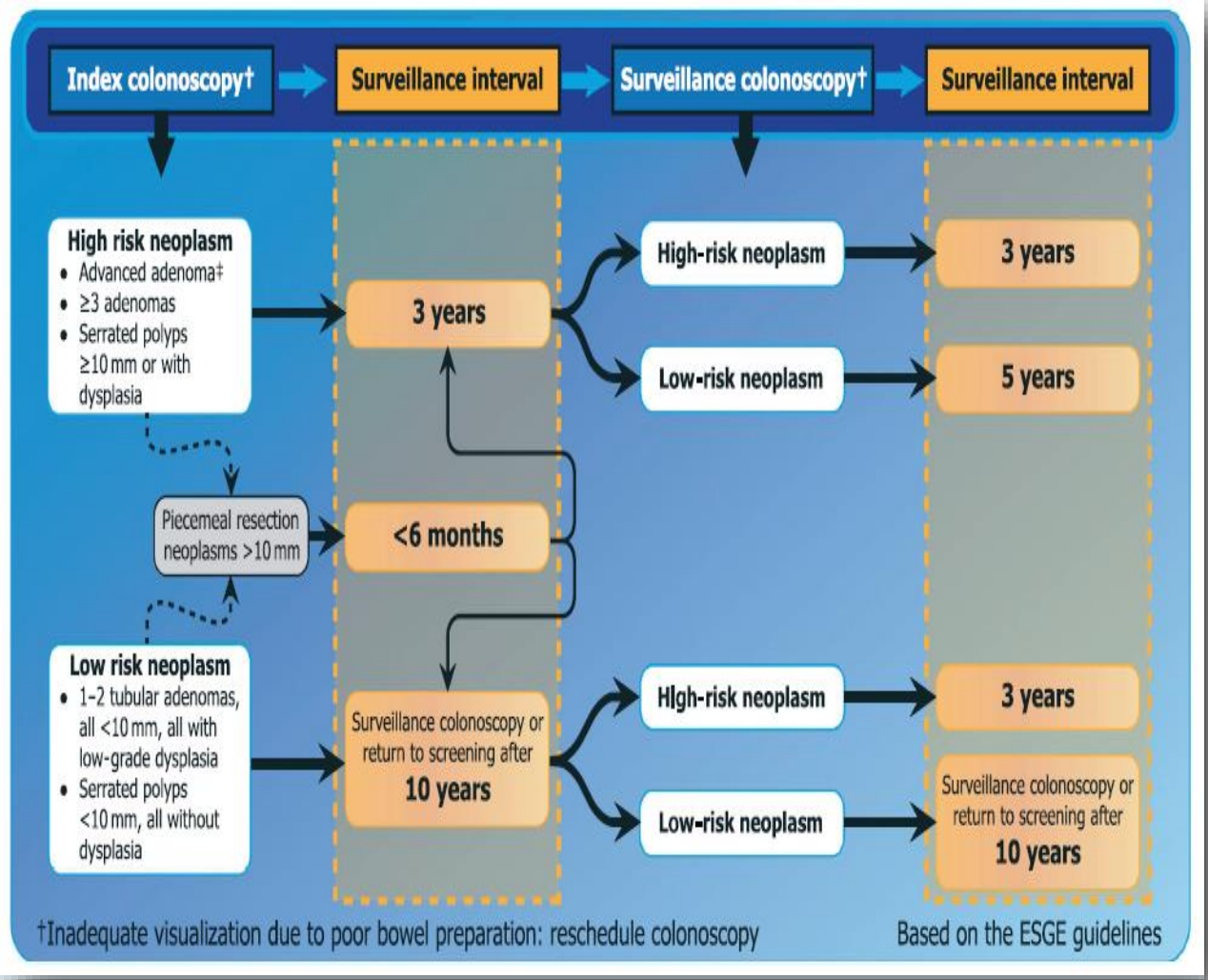


Table 2 Recommendation for surveillance intervals of serrated polyps (revised from Lieberman *et al.*[32])

Baseline colonoscopy: most advantage findings	Recommended surveillance
No polyps	10
Small (< 10 mm) hyperplastic polyps in rectosigmoid	10
Sessile serrated polyps < 10 mm with no dysplasia	5
Sessile serrated polyps ≧ 10 mm	3
Sessile serrated polyps with dysplasia	3
Traditional serrated adenoma	3
Serrated polyposis syndrome	1

JGH 32 (2017) 358–367
Am J Gastroenterol 2015; 110:1657–1664

Interval cancer 발생 줄이기

부산대학교병원 Pusan National University Hospital

Colonoscopy Quality is the Answer for the Emerging Issue of Interval Cancer !!!

Missed lesion 줄이기

Tumor biology 이해

Follow-up/Suveillance recommendation

Complete removal of the polyps

대장질지표

증간암 감소

완벽한 대장내시경

Thank you for your attention.